Melatonin and Cancer Treatment

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In 1992, the Life Extension Foundation introduced a melatonin supplement because of the broad-spectrum protective effects that this hormone had shown against age-related disease.[1] Some of this research even suggested that melatonin supplementation may extend the human life span.[2] Indeed, melatonin is so intricately involved in cell regulatory processes that scientists are now studying it as an adjunctive cancer treatment.[3,4]

These days, most people are likely to associate melatonin with a hormone that helps people sleep better or prevents jet lag.[5,6] Few people realize that melatonin is a cancer-killing hormone[7,8] that can enhance the human immune system,[9,10] protect against the toxic side effects of chemotherapy[4,11] and radiation therapy,[12,13] and improve wound healing after cancer surgery.[14,15] Even fewer are aware of ongoing clinical trials in which melatonin is being used to help cancer patients better manage their disease symptoms,[16] improve their quality of life,[17] and even increase their survival rates.[4,11]

Although the evidence demonstrating melatonin's anti-cancer effects[18] cannot be overstated, melatonin's impact on cancer treatment remains largely unappreciated. This is likely because pharmaceutical companies have little to gain by advertising the anticancer efficacy of melatonin. In Europe, where melatonin is not even readily available, many clinical trials of melatonin have been conducted.[19,20] US pharmaceutical companies, however, have shown little interest in even hosting, let alone funding, such critically important and potentially lifesaving clinical trials.

Life Extension Supports Clinical Trial

The Life Extension Foundation is collaborating with Cancer Treatment Centers of America on the first prospective, randomized clinical trial utilizing melatonin in patients with advanced lung cancer. Life Extension is providing, at no charge, high-dose melatonin and placebo supplements for this ongoing clinical trial, which will be the first in the US to examine the effect of melatonin supplementation therapy on quality of life and overall survival rates for patients with metastatic non-small-cell lung cancer.

Life Extension and the Cancer Treatment Centers of America hope to determine whether patients with advanced lung cancer suffer abnormal circadian rhythms and whether this affects their melatonin levels. The researchers hope that this trial will confirm the favorable clinical results documented by Lissoni and colleagues, whose recent European clinical studies indicate that in patients with metastatic non-small-cell lung cancer, five-year survival and overall tumor regression rates were

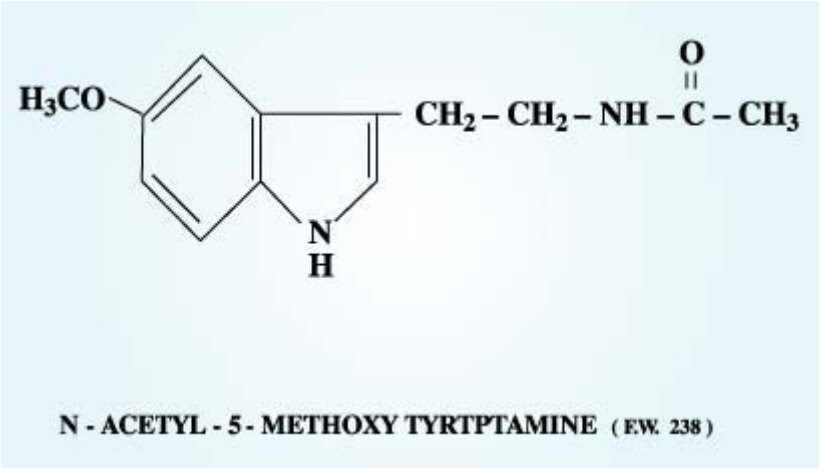


Figure 1. Structure of Melatonin (C13H16N2O2)

higher in patients concomitantly treated with melatonin than in those treated with chemotherapy alone.[4] While no patient treated with chemotherapy survived after two years, five-year survival was achieved in 3 of 49 patients treated with chemotherapy and melatonin. The researchers hope that similarly promising results could eventually convince mainstream medical practitioners to administer melatonin in combination with standard cancer treatment regimens to patients in earlier stages of cancer treatment.

Numerous, mostly European clinical studies already have examined melatonin's therapeutic benefits to patients with different types of cancer who either did not respond to standard oncological therapies[11,19] or were eligible only for supportive care (advanced cancer deemed untreatable by conventional standards).[21,22] A literature search of the PubMed database found 806 publications on "melatonin and cancer." Fifty-two articles were found concerning clinical studies utilizing melatonin in cancer patients. In this article, we will highlight and summarize some of the key studies concerning the use and mechanisms of melatonin as an adjuvant cancer therapy.

What Is Melatonin?

Melatonin (known scientifically as the indoleamine N-acetyl-5-methoxytryptamine) is a hormone with neurotransmitter modulatory activity.[23] It is produced from the amino acid tryptophan in minute quantities by the pineal gland when the eyes detect no light (i.e., in darkness or blindness, or during sleep). Melatonin also is produced by the retina[24] and, in vastly greater amounts, by the gastrointestinal system.[25] In fact, 400 times more melatonin can be found in the gastrointestinal system than in the pineal gland or bloodstream,[26] where levels typically range from 0.1 to 10 nmol/L. Melatonin receptors are present in central nervous tissues,[27] peripheral tissues,[28] and steroidogenic tissues,[29] including myometrial tissues of both pregnant and non-pregnant women.SPAN class=wwwMagTextRefNumber>30 Maternal melatonin crosses the placenta.[31]

Melatonin levels peak during the night but also increase after eating,[26] which partly explains why one may feel sleepy after a meal and why patients with advanced cancer who suffer diminished appetite or tissue wasting have been shown to have reduced levels of melatonin.[32-34] Once produced, melatonin remains in the bloodstream only a short time, on average between 20 and 90 minutes.[23,35] This is because melatonin is highly fat soluble (lipophilic) and somewhat water soluble (hydrophilic), enabling it to easily penetrate every cellular compartment (membrane, cytoplasm, and nucleus) and, as far as is known, every cell in the body.[36] Melatonin's amphiphilicity, or ability to both absorb and repel water—in conjunction with its ability to act as a weak preventive antioxidant,[37] a weak metal ion chelator,[38] and in certain circumstances, a direct free radical scavenger[39]—enables it to counteract oxidative stress within the chaotic tumor microenvironment.[40]

Melatonin's Anti-Cancer Mechanisms

Melatonin can kill directly many different types of human tumor cells.[3,41] It is a naturally produced cytotoxin, which can induce tumor cell death (apoptosis).[7,42] In instances where the tumor has already established itself in the body, melatonin has been shown to inhibit the tumor's growth rate.[43,44] Melatonin exhibits natural oncostatic activity and inhibits cancer cell growth.[45] In patients in whom cancer already has become a noticeable physical burden and produces overt symptoms, melatonin has been shown to alleviate numerous cancer symptoms[46] and to inhibit development of new tumor blood vessels (tumor angiogenesis),[47] which in turn inhibits the cancer from spreading further (metastasis).[48] Melatonin can retard tumor metabolism and development by lowering the body temperature;[35] it is a natural inducer of hypothermia. Furthermore, as an inducer of antioxidants[49] and itself a weak preventive antioxidant,[37] melatonin hinders tumor cells from participating in free radical damage to normal cells and consequently limits oxidative damage to DNA,[40] lipids,[50] amino acids, and proteins.[40]

In the unfortunate circumstance in which cancer has already overwhelmed the body's innate cancer-fighting capabilities, including the anti-cancer activity of naturally produced melatonin (levels of which are reduced in most cancer patients), supplemental melatonin may be beneficial.[17,43] Melatonin plays a critical role in the host defense system against cancer's progression by activating the cytokine system,[51] which exerts growth-inhibiting properties,[10] and by stimulating the cytotoxic activity of macrophages and monocytes.[52]

Administration of supplemental melatonin has been shown to be beneficial even in the supportive care of advanced and end-stage cancer patients: it lessens tissue wasting and diminishes weight loss, fatigue, weakness, and depression;[17,21,43,47,53] enhances immune function;[10] improves wound healing;[54] and improves quality of life and survival rates.[4] Furthermore, melatonin improves common symptoms found in both patients with advanced cancer and those undergoing chemotherapy; it counteracts anemia[55] and lymphocytopenia,[14,21] stimulates platelet production,[21] enhances appetite,[16] and diminishes cancer pain[56] (including bone pain) through its natural analgesic properties.[57] These are substantial benefits considering that approximately half of all patients diagnosed with cancer die because of poor symptom management.[58]

Melatonin and Cancer Surgery

In peri- and post-operative cancer surgery, melatonin may prove beneficial in wound healing through its natural anti-inflammatory properties.[14,59] Melatonin reduces tissue destruction during inflammatory reactions[60] by limiting hypoxia-reoxygenation-induced damage,[61] scavenging free radicals, and reducing the upregulation of pro-inflammatory cytokines,[60] such as the interleukins and tumor necrosis factor-alpha. Furthermore, surgery induces immunosuppression, which could adversely affect tumor-host interactions in cancer patients having their tumors surgically removed. As melatonin inhibits the activation of the acute inflammatory response, it may inhibit immunosuppression while contributing to an immune reaction against the tumor.[14] Moreover, melatonin can reverse the perception of pain sensation (hyperalgesia) that is secondary to inflammation associated with wound healing.[56]

In cancer patients undergoing surgical removal of gastrointestinal tract tumors, preoperative neuroimmunotherapy with melatonin and interleukin-2 (IL-2) was capable of neutralizing the surgery-induced reduction in white blood cell counts (lymphocytopenia).[14] Melatonin thus may prove to be beneficial to cancer patients who elect surgical removal of their tumors, by improving wound healing, inhibiting tissue damage, reducing pain sensation and weakness, counteracting reduced blood cell counts and anemia, and preventing immunosuppression.

Melatonin and Radiation Therapy

Radiation requires the presence of oxygen to generate free radicals to kill tumor cells. It is well established, however, that most human tumors are poorly oxygenated (hypoxic) because of blood perfusion and diffusion limitations,[62] intermittent blood flow in the tumor microcirculation,[63] and the occurrence of anemia in cancer patients (reduced hemoglobin indicates reduced oxygen levels).[64,65] In fact, radiation therapy itself usually induces anemia, which is associated with a poor prognosis in cancer patients.[66] Melatonin stimulates platelet production (thrombopoiesis)[67] and has been shown to effectively treat cancer patients with low platelet counts and anemia.[68]

Moreover, melatonin has an anti-serotonergic effect, which means that it may block the inhibition of blood flow by serotonin.[26] This consequently may increase blood flow and allow restoration of the microcirculation, which is compromised in the tumor microenvironment.[69] Melatonin may improve the blood supply to the tumor, increasing tumor oxygen levels and thus increasing radiation-induced tumor cell death (by overcoming radio-resistance).[70] In addition, melatonin is lipid soluble and can presumably cross the blood-tumor barrier as it does the blood-brain barrier.[71] Melatonin may further increase the delivery of radiation (and chemotherapeutic drugs) to poorly oxygenated regions within the tumor microenvironment, consequently increasing the effectiveness of these anti-cancer modalities. Radiation, which frequently causes inflammation of the mucosa (mucositis), may substantially reduce melatonin levels in the body[13] by damaging the mucosa of the gastrointestinal tract where melatonin is known to be localized.[26]

A radioneuroendocrine approach utilizing radiotherapy with melatonin supplementation in brain glioblastoma patients showed that the likelihood of survival at one year was significantly higher in those who received melatonin with radiotherapy versus radiotherapy alone.[12] It recently has been suggested that melatonin may diminish the risk of hypoperfusion-induced cerebral ischemia.[72] Therefore, melatonin supplementation may prolong the survival of patients undergoing radiotherapy.[3] Melatonin also may provide relief from the inherent detrimental side effects of radiation treatment[73] (including toxicity to the heart, kidneys, and nerves—cardiotoxicity, nephrotoxicity, and neurotoxicity, respectively), immune suppression, pain, anemia, fatigue, and sleep disturbances.[12] Melatonin is a safe and effective facilitator of tissue repair processes, required for recovery from radiation-induced injury,[74] and thus offers a promising co-treatment approach for patients undergoing radiation therapy for cancer.

Summary of Studies Using Melatonin
Lissoni's Phase II Randomized Clinical Trial Results

				One-Year Survival		
Tumor Type	Patient Number	Basic Therapy	Melatonin Dose	Melatonin	Placebo	Level Of Significance
Metastatic Non-Small-Cell Lung	100	Chemotherapy	20 mg	5-year survival 6%	5-year survival 0%	N/A
Metastatic Non-Small-Cell Lung	63	Supportive Care Only	10 mg	5-year survival 6%	Under 1%	<0.05
Glioblastoma	30	Conventional Radiotherapy	10 mg	43%	Under 1%	<0.05
Metastatic Breast	14	Tamoxifen	20 mg	64%	36%	<0.01
Brain Metastases	50	Conventional Radiotherapy	20 mg	38%	12%	<0.05

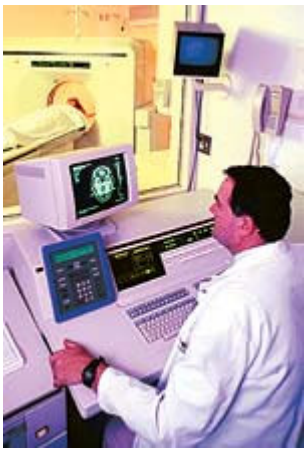
Metastatic Colorecta	50	IL-2	40 mg	36%	12%	<0.05<0.05
Metastatic Non-Small-Cell Lung	60	IL-2	40 mg	24%	19%	<0.05

Adapted from Life Extension (March 2002). Originally compiled by Cancer Treatment Centers of America.

Melatonin and Chemotherapy

Chemotherapy, through immunosuppressive and cytotoxic actions, exerts detrimental effects on patients' physiological anti-cancer defense mechanisms. Melatonin, by improving immune status,[52,75] has been shown to prolong survival and increase performance status in those undergoing chemotherapy. In conjunction with various chemotherapy regimens, melatonin has provided patients with a significant advantage over chemotherapy alone by increasing five-year survival rates, improving quality of life, and increasing the therapeutic effectiveness of many chemotherapeutic agents,[76] while lessening or eliminating their negative and potentially detrimental side effects on normal healthy cells and tissues.[4,77,78] Melatonin reduced chemotherapy-induced cardiotoxicity, neurotoxicity, nephrotoxicity, thrombocytopenia (reduced platelet counts), stomatitis (inflammation of mouth), and asthenia (weakness), and improved response in cancer patients.[79,80]

Melatonin should be seriously considered in combination with extremely toxic chemotherapy regimes—such as anthracyclines (adriamycin),[81] cyclosporine, cytarabine,[78] IL-2, cisplatin,[55,79] 5-fluorouracil,[75,82] and methotrexate[78,82]—to reduce the incidence of their well-established side effects,[80] which include but are not limited to mucositis and heart and liver toxicity.[75] Melatonin recently has been shown to prevent methotrexate-induced liver and kidney toxicity in animals.[83] It should be remembered that fasting reduces melatonin levels, typically within two days,[84] suggesting that nausea, vomiting, and reduced appetite—side effects of chemotherapy—may reduce melatonin levels.



Melatonin and Chronotherapy

Because of the circadian rhythm dictated by the body's melatonin levels, some types of chemotherapy work best if administered at an appropriate time of day, and are thus termed "chronotherapy."[3] The daily rhythm of melatonin exerts a "chronobiotic" effect and, as a circadian mediator, melatonin delivers the circadian signals to melatonin targets, including the internal body clock (in the suprachiasmatic nucleus).[85] Chronotherapy is associated with maximum patient tolerability, tumor susceptibility, and attempts to improve the efficacy of treatment and the quality of patients' lives. It takes advantage of asynchronies in growth rate between normal and tumor cells that are regulated by the circadian rhythm, thus minimizing damage to the patient and maximizing drug toxicity to tumor cells.

The growth of tumor cells may intrinsically follow a tumor-specific rhythm. It may be possible to modulate this rhythm by manipulating cancer patients' melatonin levels.[86] The local effect produced on the circadian clock could thus modulate the circadian rhythm.[87] Slow-growing tumors could more likely be controlled by the patients' circadian clock, whereas fast-growing or advanced-stage tumors may have altered circadian rhythms even though they are not temporally disorganized masses. High doses of melatonin are necessary to induce a phase-shifting effect on the circadian rhythm.[88] Melatonin thus may have a unique ability to control the biological clock, consequently suppressing malignant growth and increasing the efficacy of cancer therapies. Chronotherapy has been shown to increase the survival time in children with acute lymphoblastic leukemia.[89]

Melatonin and Hormonal Therapy

Melatonin levels in cancer patients have been correlated with tumor aggressiveness and progression.[90,91] A high percentage of women with estrogen-receptor-positive breast cancer have low plasma melatonin levels.[92] Conversely, melatonin inhibits human breast cancer cell growth[45] and reduces tumor spread and invasiveness in vitro.[48] Indeed, it has been suggested that melatonin acts as a naturally occurring anti-estrogen on tumor cells, as it down-regulates hormones responsible for the growth of hormone-dependent mammary tumors.[93]

Melatonin differs from the classic anti-estrogens such as tamoxifen in that it does not seem to bind to the estrogen receptor or interfere with the binding of estradiol to its receptor.[94] Moreover, melatonin can increase the therapeutic efficacy of tamoxifen[95] and biological therapies such as IL-2.[96] How melatonin interferes with estrogen signaling is unknown, though recent studies suggest that it acts through a cyclic adenosine monophosphate (cAMP)-independent signaling pathway.[93] It has been proposed that melatonin suppresses the epidermal growth factor receptor[3] and exerts its anti-proliferative effects by inducing differentiation[97] as proposed for melanoma cells.[98]

Regardless of the mechanism, in tumorigenesis studies melatonin reduced the incidence and growth rate of breast tumors and slowed breast cancer development.[99] Furthermore, prolonged oral melatonin administration significantly reduced the development of existing mammary tumors in animals.[100] In a metastatic hormone-refractory prostate cancer patient, oral melatonin (5 mg/day) induced disease stabilization for six weeks.[44]

Melatonin Dosage for Cancer Patients

While the optimal dose of melatonin for treating different types of cancer has not yet been established, the many clinical studies by Lissoni and colleagues have shown that doses of 10-50 mg of melatonin nightly are beneficial to cancer patients.

Those recently diagnosed with slow-growing or early-stage cancer may wish to consider supplementing with 3 to 6 mg melatonin nightly; the latter dose may be reserved for early-stage cancer patients who suffer from disturbed sleep patterns. Because most clinical studies have shown that patients with late-stage, advanced, or untreatable cancer, or those with cancer metastasis, benefit from supplementation with 20 mg of melatonin, such patients may wish to consider supplementing with between 6 and 50 mg of melatonin nightly, depending on plasma melatonin levels.

Physicians should be strongly encouraged to

Night Light, Melatonin, Meditation, and Cancer Incidence

prescribe substitutional melatonin therapy to cancer patients with depressed melatonin levels.

Low levels of melatonin have been associated with breast cancer occurrence and development. Women who work predominantly at night and are exposed to light, which inhibits melatonin production and alters the circadian rhythm, have an increased risk of breast cancer development.[101] In contrast, higher melatonin levels have been found in blind and visually impaired people, along with correspondingly lower incidences of cancer compared to those with normal vision, thus suggesting a role for melatonin in the reduction of cancer incidence.[102]

Light at night, regardless of duration or intensity, inhibits melatonin secretion and phase-shifts the circadian clock, possibly altering the cell growth rate that is regulated by the circadian rhythm.[103] Disruption of circadian rhythm is commonly observed among cancer patients[104,105] and contributes to cancer development and tumor progression.[106] Cancer alters neuroendocrine system function in such a way that melatonin levels are lower in patients with non-small-cell lung cancer.[107] Indeed, the circadian rhythm of melatonin is also altered in advanced gastrointestinal malignancies, such as colorectal, gastric, and pancreatic cancer, with respect to healthy humans.[108]

Deregulation of many circadian clock functions in the human body—including blood pressure, temperature, hormones, sleep-wake pattern, immune function, and digestive activity—has been used as an independent prognostic factor of survival time and tumor response for patients with certain metastatic cancers.[109] The circadian rhythm alone is a statistically significant predictor of survival time for breast cancer patients.[110]

Several studies have shown that the circadian clock is involved in tumor suppression at the systemic, cellular, and molecular levels, and that cancer should no longer be treated as a local disorder. For instance, the circadian clock regulates the immune response. Disruption of circadian rhythms could therefore lead to immunosuppression, which could disrupt cancer cell immunosurveillance and promote tumor development; however, melatonin as a circadian mediator can target the endogenous clock[86] and has been shown to inhibit immunosuppression.[111]

The phenomenon of light at night regulating melatonin levels may explain the spontaneous tumor regression reported to occur through meditation alone in cancer patients (when the eyes are closed and detect no light).[112-114] The regular practice of meditation is associated with increased physiological levels of melatonin.[115,116]

Pharmacological doses of supplemental melatonin can resynchronize individuals shown to have disrupted circadian rhythms,[36,117] such as night-shift workers.[118] Thus, cancer patients with endogenously depressed melatonin levels may benefit from both meditation and substitutional melatonin therapy, to improve quality of life[119] while potentially inhibiting tumor growth and spread.

Melatonin and Advanced Cancer

Numerous clinical studies by Lissoni and colleagues have shown that melatonin adjuvant therapy favorably influences the course of advanced cancer, leading to an improved quality of life and increased survival.[17,21] In cancer patients with untreatable advanced solid tumors, melatonin significantly lowered the frequency of catabolic wasting (cachexia), weakness (asthenia), low platelet (thrombocytopenia), and white blood cell counts (lymphocytopenia) compared to patients who received supportive care only. Melatonin improved disease stabilization and increased survival percentages at one and five years.[4,21]

Melatonin deficiencies in advanced cancer patients may be due to altered circadian rhythm (disturbed sleep patterns), cancer-related anorexia-cachexia, and reduced food intake as melatonin is produced by the enterochromaffin cells in the gastrointestinal tract in response to feeding.[25] Melatonin supplementation in turn increases appetite,[26] diminishes tissue wasting,[21,46] and restores sleep continuity in those with cancer.[5,71,120] Administration of melatonin to patients with advanced cancer who have only short expected survival times results in some cases in disease stabilization and improvement of performance status.[17,43,119]

Melatonin Supplementation and Cancer

Extrapolating the reduced melatonin levels observed in aging humans[121,122] to the cellular level, one might expect to find less melatonin at the cellular level in tumors[32,107] compared to normal healthy cells if tumor cells “age” (because of their increased growth rate) more rapidly than normal healthy cells. The potentially lower melatonin levels in tumor cells could possibly be normalized by melatonin supplementation, which in turn would be expected to lead to a negative growth advantage in the tumor microenvironment and therefore inhibit tumor growth. Melatonin levels are depressed in individuals with cancers of different origins during the phase of primary tumor growth,[110] whereas normal melatonin levels may be found when remission occurs.[123]

In summary, results of the numerous clinical studies in patients undergoing standard anticancer therapies—including chemotherapy, immuno-hormonal therapy, radiation therapy, and cancer surgery—suggest that individuals with cancer should consider melatonin supplementation under a physician’s supervision. While melatonin may be obtained through diet and enter the bloodstream, sources of natural melatonin production, such as food intake, gastrointestinal bacteria, and bile, may be reduced in cancer patients. Taken together, these factors, in conjunction with the short half-life of melatonin, provide a good basis for recommending melatonin supplementation as an adjuvant therapy for cancer.

With the current level of evidence on the multidisciplinary anticancer actions of melatonin, Life Extension believes that physicians should be strongly encouraged to prescribe melatonin to patients with certain tumor types on diagnosis or during early stages of tumor development. Continued research and clinical trials are imperative to further define melatonin’s role in the management of cancer’s physical and psychological symptoms and in the adjuvant treatment of cancer patients. Sadly, due to a lack of commercial opportunities, we are unlikely to see further clinical trials with melatonin in the US, other than those sponsored by foundations such as Life Extension.

Much remains to be learned about how practical therapeutics will be achieved with melatonin supplementation. Despite the many practical hurdles to the use of melatonin in the adjuvant treatment of cancer patients, particularly in the US, we remain hopeful that the overwhelming proof of melatonin’s efficacy will eventually drive its use in clinical applications.

Contraindications and Dosage

One study reported no contraindications to melatonin use.[158] Because of unknown risk, pregnant and nursing women should take melatonin only under the close supervision of a

physician or not at all.[158] Some researchers have suggested that people with allergies, asthma, autoimmune diseases, and immune-system cancers, such as leukemia and lymphoma, should use melatonin with caution. Clinical studies have shown, however, that in leukemia and lymphoma patients, simultaneous administration of melatonin with IL-2 is beneficial in providing disease stabilization and in prolonging survival time.[53]

Who's at Risk for Melatonin Deficiency?

- Apart from those confronted with cancer, melatonin-deficient individuals may include:
- the elderly, geriatrics, and those with age-related disease[117,139,145]
- shift workers, individuals exposed to light at night, and insomniacs[39,146]
- airline pilots, flight attendants, and frequent transcontinental flyers [6,147]
- individuals with occupations involving high electromagnetic field exposure, including telephone or electric-line workers[148]
- those with pineal disease,[149] pinealectomised individuals (those without a pineal gland),[150] or those with suprachiasmatic nucleus involvement[117]
- quadriplegics[151]
- post-gastric[26] or post-spinal-cord surgery patients[151,152]
- anorexics, bulimics, and those with poor appetite or subject to frequent vomiting136 or with irritable bowel syndrome, diarrhea, or ulcerative colitis[25]
- individuals undergoing total parenteral nutrition (intravenous nutrition),[153] and those who fast chronically[84]
- those who suffer from delayed sleep phase syndrome, circadian rhythm variations, fibromyalgia, depression, or anxiety (treated by benzodiazepines)[72,136, 154]
- females who suffer cramping (uterine contractile disturbances) associated with menstruation,[30] as melatonin has been shown to block prostaglandin production[155] and depress spontaneous uterine contractility[156]
- individuals on blood pressure medication, such as beta-blockers, statins, or calcium channel blockers.[157] Most medications prescribed to lower blood pressure also inadvertently reduce serum melatonin levels, including beta-blockers, calcium channel blockers, and calcium antagonists. An estimated 40% of individuals who take beta-blockers have sleep disorders that may be easily remedied by taking melatonin. It has been suggested that, in clinical trials, melatonin should be combined with statins to reduce the free-radical-mediated side effects of these cholesterol-lowering drugs.[158]

Studies in humans have shown melatonin toxicity to be remarkably low with no serious negative side effects even at high doses (3 to 6.6 g) administered over a period of 35 days.[159,160] Nevertheless, minor reactions to melatonin supplementation such as sleepiness, vivid dreams, headache, abdominal pain, and nausea have been reported to occur occasionally in a small proportion of individuals.[158] Excess melatonin production has rarely been seen except in polycystic ovary disease.[161] More recently, an observational study found elevated serum melatonin levels in individuals with nocturnal asthma.[162]

Sources of Melatonin

Melatonin is present in all living organisms, including microalgae (green algae), bacteria, fungi, plants, small crustaceans (certain prawns and crayfish), fish, animals, and humans.[163] Natural sources of melatonin, not standardized to provide a defined concentration, and with possible contaminants, also include medicinal plants such as feverfew (Tanacetum parthenium), St. John's wort (Hypericum perforatum), and huang-qin (Scutellaria baicalensis),[122,164] sometimes

reaching levels of several nanograms per gram[165] and possibly contributing to the therapeutic efficacy of the respective herbs.

High melatonin concentrations are found in seeds and some fruits such as tart cherries, bananas, and tomatoes.166,167 Melatonin also is found in food sources such as oats, rice bran, sweet corn, wheatgrass juice, and ginger. It has been shown that dietary melatonin (from plant sources) directly elevates the circulating level of melatonin in the body,[168] as does smoking marijuana.[169]

The building blocks for natural melatonin production in the body include sufficient amounts of vitamin B6, vitamin B3 (niacinamide), and most important, the amino acid tryptophan, which is found in high quantities in foods such as nuts (soy, almonds, and peanuts,), seeds (pumpkin and watermelon), spirulina, beans, and tofu.

Who Should Supplement with Melatonin?

Melatonin is widely accepted for the treatment of sleep disorders and circadian rhythm disturbances,[132,133] and is particularly effective for certain types of insomnia and sleep disorders in the elderly.[134] Melatonin can facilitate the discontinuation of commonly prescribed sleeping medications, such as benzodiazepine therapy.[135, 136] The “chronobiotic” effect of melatonin has been used to help re-synchronize individuals shown to have disrupted circadian rhythms (for example, blind people),[88] in “delayed sleep phase” syndrome, night-shift work, and jet lag.[118] In fact, the best clinical indication for melatonin is for alleviating jet-lag symptoms, particularly if taken at the bedtime of the arrival destination.[118] In children, melatonin has been reported to be beneficial for treating colic, diarrhea, sepsis,[50] and asphyxia.[71,137]

- In advanced age, melatonin supplementation should be considered for the following reasons:
- Melatonin production declines with age,[121] and it has been shown that the aged have lower blood levels of melatonin. Elderly women have higher levels of melatonin compared to elderly men, which may be one reason why women live longer than men.
- Aged individuals with early neuropathological changes in the temporal cortex, where the Alzheimer’s disease process starts, have lower cerebrospinal fluid levels of melatonin.[138]
- The preventive antioxidant activity of melatonin may counteract free-radical-mediated degenerative diseases typical of the aged.[139-141] Melatonin has been shown to be beneficial in the treatment of Alzheimer’s disease.[142,143]
- If aging is indeed a consequence of accumulated free radical damage, then the unique electro-reactive properties and intracellular distribution of melatonin should be advantageous in deferring the signs of aging.[117]
- Melatonin has beneficial effects on sleep disorders,144 which frequently afflict the aged.[134]

Melatonin Availability

Melatonin is available either as an over-the-counter drug or food supplement in the US, Argentina, Poland, and China. Although theLife Extension Foundation’s melatonin supplements are not registered as drugs, their purity has been certified and verified by an independent laboratory for the purposes of the ongoing lung cancer clinical trial. Unfortunately, this is not the case with many of the other readily available melatonin supplements, as certification is not mandated for food substances or additives.

For now, melatonin remains a relatively inexpensive nutritional supplement not yet controlled by the FDA or any other corporate or regulatory body. Interestingly, there has been mention of categorizing melatonin as a vitamin, which could be beneficial in compelling the medical

establishment to finally recognize its importance. On the other hand, many pharmaceutical companies have started to patent therapeutic uses of melatonin: a Dutch company has patented a composition for intranasal melatonin administration, a French company has patented a melatonin agonist for the purpose of treating depression and sleep disorders, and an Israeli company has patented a method for treating or preventing symptoms of tardive dyskenisia by melatonin administration.

When to Take Melatonin

Melatonin should probably be taken 30 minutes to one hour before sleeping. Slow-release melatonin preparations may benefit those with various types of insomnia, as the oral bioavailability of melatonin is approximately 15%.[170] Exposure to light at night, however, regardless of the duration or intensity of the light, can fully suppress or decrease melatonin levels.[171]

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