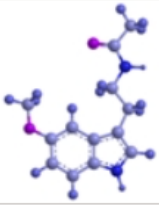

Melatonin

SCIENTIFIC NAME
N-Acetyl-5-Methoxytryptamine

FAMILY

CAUTION: Melatonin should not be confused with a chemical with a similar name, known as Melanotan.

Other Common Names

- 5-Methoxy-N-Acetyltryptamine, MEL, Melatonina, Mélatonine, MLT, N-Acétyl-5-Méthoxytryptamine, Pineal Hormone.

Overview

Melatonin is an endogenous hormone produced in the brain by the pineal gland (1773,96314,96318,96320). Melatonin regulates the body's circadian rhythm, endocrine secretions, and sleep patterns (1773,7043).

WARNINGS

Most commercial melatonin that is found in supplements is synthesized in the laboratory. However, in rare cases it can be derived from animal pineal gland. Melatonin from animal sources should be avoided due to the possibility of contamination (1772,8266). Melatonin supplements have been shown to have high lot-to-lot variability in content, with some products containing almost five times above the amount indicated on the label. In addition, some melatonin supplements may be contaminated with serotonin (108144).

Because of its potential for causing daytime sleepiness, people should not drive or use machinery for 4-5 hours after taking melatonin (1772).

Coronavirus disease 2019 (COVID-19): Despite some laboratory data suggesting benefit, there is no good evidence from clinical trials to support the use of melatonin for COVID-19. Recommend healthy lifestyle choices and proven prevention methods instead.

Safety

LIKELY SAFE ...when used orally and appropriately, short-term or as a single dose. Melatonin seems to be safe when used up to 8 mg daily for up to 6 months. Melatonin 10 mg daily has been used safely for up to 2 months (1049,1068,1077,1085,1738,1754,5854,5855,5857,12226), (14283,15005,62850,89502,89503,88285,88289,88293,88294,88295)(88296,88299,89508,89510,89511,96313,96314,96316,96317,96319)(96321,97438,99345,103484,106301,106303,107811,110286,110299). ...when used topically and appropriately (1066,1768,1769,4713,4714,96314).

POSSIBLY SAFE ...when doses of up to 8 mg daily are used orally and appropriately for longer than 6 months, doses

of 10 mg daily are used for longer than 2 months, or doses of 50 mg daily are used for up to 5 days (7040,7043,62435,106296,107811). There is some evidence melatonin can be used safely in doses of up to 10 mg daily for up to 2 years in some patients (7040,7043,62435). ...when used intravenously under the supervision of a healthcare professional. A one-time dose of intravenous melatonin combined with a single bolus of intracoronary melatonin has been used with apparent safety in one clinical trial (96324).

CHILDREN: **POSSIBLY SAFE** ...when used orally in low doses, short-term (9980,15034,62792,88282,88283,88286,88288,95748,96318,97434)(97439,97446,106293,110292). Although melatonin has been safely used in clinical research in doses up to 12 mg daily (88283), it is often advised that daily doses of melatonin be limited to 3 mg daily for children and infants 6 months or older and 5 mg daily for adolescents (95746). There is some concern that taking melatonin might adversely affect gonadal development in children (1739,1740,1742,1743). While some evidence suggests that long-term use of melatonin in children may delay puberty, the available research includes only three small, observational studies with incomplete follow-up and poor measures of pubertal timing (95747). Although rare, pediatric overdose with melatonin has resulted in hospitalization, mechanical ventilation, and death (108145). Due to potential risks, melatonin should be used only in children with a medical reason for use; it should not be used to promote sleep in otherwise healthy children. There is insufficient reliable information available about the safety of melatonin when used long-term.

PREGNANCY: **POSSIBLY UNSAFE** ...when used orally or parenterally in high doses or with frequent use. High doses of melatonin 75-300 mg daily seem to inhibit ovulation, causing a contraceptive effect (769,1740,6002,8271,95728). Advise pregnant patients and patients wishing to become pregnant to avoid using melatonin frequently or in high doses.

There is insufficient reliable information available about the safety of melatonin in lower doses during pregnancy. Some research shows that taking melatonin 2 mg daily does not affect anterior pituitary hormone levels in females who are not pregnant; this suggests that low doses may not have a contraceptive effect (62898). Other research shows that taking melatonin 3 mg daily during the follicle stimulating stage of in vitro fertilization does not negatively impact pregnancy rates (62818,62819,88297,89512,88297). However, it is not known if melatonin is safe for use throughout pregnancy (95729). Until more is known about the safety of melatonin, avoid using during pregnancy.

LACTATION: Insufficient reliable information available; avoid using.

Adverse Effects

General: Orally, melatonin is generally well tolerated.

Most Common Adverse Effects:

Orally: Dizziness, drowsiness, headache, and nausea.

Serious Adverse Effects (Rare):

Orally: There is concern that melatonin may increase the risk for seizure.

- ### Cardiovascular

  Melatonin might increase levels of very low-density lipoprotein (VLDL) cholesterol and triglycerides (62176). Several rare or poorly described cases of abnormal heart rhythms, palpitations, fast heart rate, or chest pain

have been reported. However, in these cases, the patients were taking other drugs that could account for the symptoms, and melatonin was not thought to be the cause (1079,9181,62776,62789,63067).

- **Dermatologic**

Papular skin rash and pruritus has been reported with melatonin use. However, the effect was generally mild and did not require cessation of melatonin treatment (62450,62754,109696), and had similar rates as placebo (96316). Cutaneous flushing has also been reported (62770,62914). Two cases of fixed drug eruption on the genitalia have been reported for patients who used oral melatonin (Nature's Bounty Natural melatonin) for preventing jet lag (88284).

- **Endocrine**

A case of gynecomastia (increased breast size) has been reported for a 56 year-old patient with amyotrophic lateral sclerosis (ALS) who used oral melatonin, long-term (89430). Also, reduced sperm concentration and sperm motility has been reported for two men who used oral melatonin 3 mg daily for 6 months. Improvement in sperm quality was observed for only one of the two men following melatonin cessation (62231).

- **Gastrointestinal**

Orally, melatonin may cause nausea (62384,62770), abdominal cramps, or mild abdominal pain (62450,62754,62914,96316), diarrhea (62804,62811,62914), constipation (96316), or decreased appetite (62345,62792). Often these symptoms occur during the first few days of treatment and subside after a few days (62804). In some cases, rates of symptoms are similar between melatonin and placebo (96316). Less often, melatonin has been reported to cause abnormal feces (62450), odd taste in the mouth (1070), or reflux esophagitis (1745) when used orally. A case of exacerbated symptoms of Crohn disease, including increased diarrhea and abdominal cramps, has been reported for a patient who took oral melatonin 3 mg at bedtime for 4 days. Symptoms resolved within 24 hours of melatonin treatment cessation (62218).

- **Genitourinary**

Orally, melatonin may increase enuresis in adults and children (58685,62450,62710,62770,62804,62804,62811). In perimenopausal adults, melatonin has caused a resumption of spotting or menstrual flow (11806). Decreased libido has been noted for one patient treated with melatonin 3 mg daily for 8 weeks (15216).

- **Hematologic**

A case of nose bleed has been reported with oral melatonin (62450). Some melatonin preparations contain contaminants that are associated with eosinophilia-myalgia syndrome (9715,9716).

- **Hepatic**

A case of autoimmune hepatitis has been reported for a patient who took melatonin orally to treat insomnia (63037).

- ## Musculoskeletal

Preliminary clinical evidence shows that a single dose of melatonin 3 mg may increase fall risk due to increased postural swaying while standing on one or both feet in healthy adults ages 60-71 years (97442). A single case of ataxia has been reported for an 81-year-old female who used melatonin for 4 days (9181). Weakened muscle power has been reported for two patients treated with melatonin 5 mg in the evening (62456). Some melatonin preparations contain contaminants that are associated with eosinophilia-myalgia syndrome (9715,9716).

- ## Neurologic/CNS

Orally, melatonin may cause migraine-like headache (1070,1077,15034,62384,62450,62710,62754,62804,62792,62914,88288,88293,88294,96318)(106297) or dizziness (62345,62384,62450,62456,62770,62784,62792,62804,62811,89510)(110297). Often these symptoms occur during the first few days of treatment and subside after a few days (62804). Melatonin may also cause drowsiness or fatigue when taken orally (1077,8273,15216,62384,62456,62784,62804,62811,88288,89510,96314,96316,96318,97446)(106293,106297). These symptoms appear to be more common if melatonin is taken in the morning or at very high doses (greater than 50 mg) (8269,62874). A case of excessive drowsiness has been reported when melatonin was combined with citalopram, nortriptyline, and oxycodone. Sedation improved with discontinuation of melatonin (96315). Indiscriminate use of melatonin may cause irregular sleep-wake cycles to occur (62998). Less commonly, melatonin may also cause behavior worsening (62811), confusion or disorientation (63014,63067), nighttime awakening (62710,62811), mood swings or agitation (96318), stereotypy (96318), excitement before bedtime (62811), nightmares or more intense dreams (62401,62462,62780,62784,88283), feelings of a "rocking" sensation (62155), or reduced alertness when taken orally.

A case of generalized epilepsy has reportedly occurred after treatment with melatonin for 4 months (9708). Also, some case reports raise concerns about increased risk of seizure with melatonin treatment, but conflicting evidence suggests that melatonin may decrease the risk of seizures (1699,8248,9695,9697,9744,9746,62123,62256,62384,62754)(63070,63071,89431). One patient experienced hyponatremia with confusion and seizures after taking prolonged-release melatonin 2 mg. However, malnutrition and cannabis abuse were also thought to contribute to this reaction (96321).

Although there is concern that melatonin might affect cognitive function in healthy adults, research in humans suggests that oral or topical melatonin do not impact most measures of cognitive function (97442,97448).

- ## Psychiatric

Orally, melatonin may cause mood changes, including dysphoria (sadness) (1764), dips in mood (62345,62450,62792), nervousness (62784), or transient depression (1077). Delusions and hallucinations have also been reported in clinical research (62347). An isolated incident of aggressiveness was also noted in a child diagnosed with attention deficit-hyperactivity disorder (ADHD) who took melatonin in combination with methylphenidate (9980). Severe irritability has been reported in two children with autism spectrum disorder who had abruptly discontinued melatonin due to the completion of a clinical trial (106293).

Effectiveness

LIKELY EFFECTIVE

Delayed sleep phase syndrome (DSPS). Oral melatonin shortens the time needed to fall asleep in children and adults with DSPS.

Details: Most clinical research shows that taking melatonin orally reduces the length of time needed to fall asleep and advances sleep onset time in young adults and children with DSPS (8244,12226,15005,62714,62792,63055,88288,88290,89509). In adults, 0.3-5 mg daily for up to 9 months has been used (8244,62714,62792,63055,88290,89509). In children, 1-6 mg before bedtime for up to one month has been used (62714,62792,89509). In addition to improving sleep, melatonin also improves measures of quality of life such as mental health, vitality, and bodily pain in young adults with DSPS (8244,12226,15005). However, relapse to pre-treatment sleeping patterns seems to occur within one year after stopping supplementation (63048).

Non-24-hour sleep wake disorder. Oral melatonin improves non-24-hour sleep wake disorder in blind children and adults.

Details: Taking oral melatonin 0.5-4 mg daily in children and 0.5-10 mg daily in adults for up to 6 years helps improve circadian rhythm sleep disorders in blind children and adults (1082,1744,1749,6585,62346,62350).

POSSIBLY EFFECTIVE

Beta blocker-induced insomnia. Oral melatonin seems to improve sleep in patients with insomnia related to the use of beta-blockers.

Details: Beta-blockers such as atenolol and propranolol seem to decrease endogenous melatonin levels (1780). This might result in insomnia as a side effect. Clinical and preclinical research shows that taking a melatonin supplement might decrease the insomnia caused by beta-blockers (1062,89502). Taking melatonin 5 mg at night after taking atenolol 100 mg appears to attenuate the changes in sleep onset latency, total wake time, and wakefulness after sleep onset when compared with taking atenolol 100 mg alone (1062). Also, in patients taking atenolol or metoprolol, taking melatonin 2.5 mg one hour before bedtime for 20-28 days increases total sleep time by 13-37 minutes and decreases sleep latency by 8-14 minutes when compared with placebo (89502).

Cancer. In patients with various types of cancer, most research shows that oral or combined intramuscular/oral melatonin in combination with chemotherapy or other treatments seems to improve tumor regression and survival rates.

Details: There is some evidence that taking combined high-dose melatonin with conventional chemotherapy or with interleukin-2 (IL-2) might improve tumor regression rate in patients with breast, lung, kidney, liver, pancreatic, stomach, or colon cancer (1692,5854,5855,5857,7040,7043,8268,62407,62844). Melatonin plus chemotherapy in patients with metastatic solid tumors seems to increase the regression rate and one-year survival rate by about 40% to 50% when compared with chemotherapy alone (7040,62407,62844,89504). The addition of melatonin also seems to help reduce chemotherapy toxicities, including hematologic complications, cachexia, asthenia, and neuropathy (8268,62844,89504). There is also some preliminary evidence that melatonin alone, orally or intramuscularly, might improve stabilization rate and possibly one-year survival rate in patients with resistant or untreatable neoplasms of the lung, liver, pancreas, colon, breast, or brain (1080,1688,1693,2566). Also, when used in combination with radiotherapy, high-dose melatonin seems to increase the survival time and percent survival in patients with brain glioblastomas when compared with radiotherapy alone (62991). However, high-dose melatonin treatment does not seem to improve the survival of patients with brain metastases who receive radiation therapy (62455). Melatonin 10-40 mg daily has been used in most clinical trials (1080,1692,1693,2566,5854,5855,5857,7040,7043,8268)(62455,62844,62991,89504). In one study, melatonin 20 mg intramuscularly daily for 2 months, followed by oral melatonin 10 mg daily as maintenance, was used (1688).

The effect of melatonin on quality of life and sleep quality in patients with cancer has also been investigated. A meta-analysis of six clinical trials shows that taking melatonin 20 mg daily does not improve sleep quality or quality of life when compared with a control, usually placebo. The duration of studies varied widely; from a period of 7 days or until death. However, there was a modest effect of melatonin on symptoms of depression in patients taking it for at least 14 days or those who underwent surgery (109697).

Emergence delirium. Oral melatonin seems to be beneficial for reducing sevoflurane-induced agitation in children. It is unclear if oral melatonin is beneficial for adults undergoing surgery.

Details: A meta-analysis of clinical research in perioperative adults shows that taking melatonin 3-5 mg or ramelteon 8 mg orally daily for 1-7 days reduces the risk of emergence delirium by 59% when compared with placebo or no treatment. However, the validity of these results is limited by high heterogeneity (112053).

Clinical research in children aged 3-9 years shows that taking melatonin 0.3 mg/kg as part of a multimodal anxiolytic strategy reduces the incidence of sevoflurane-associated emergence delirium when compared with placebo or midazolam 0.3 mg/kg. Emergence delirium occurred in 27% of those children given melatonin, compared with 50% of those given placebo and 56% of those given midazolam (106292). In addition, a meta-analysis of three small clinical studies in children aged 2-9 years shows that taking melatonin 0.05-0.5 mg/kg 40-45 minutes prior to sevoflurane reduces the incidence of agitation when compared with placebo, with inconclusive outcomes when compared with midazolam and dexmedetomidine. A sub-group analysis indicates that doses of melatonin 0.2 mg/kg or greater may be most effective (97440). However, taking melatonin 0.5 mg/kg before surgery is 55% less effective than intranasal dexmedetomidine 2 mg/kg for reducing the incidence of sevoflurane-associated emergence delirium (109701).

Hypertension. Oral controlled-release melatonin seems to reduce blood pressure by a small amount in patients with hypertension. Immediate-release melatonin may not have the same effect.

Details: Controlled-release melatonin 2-24 mg, taken before bedtime for up to 4 weeks, seems to lower systolic blood pressure (SBP) by 4-6 mmHg and diastolic blood pressure (DBP) by about 4 mmHg in individuals with essential hypertension or high blood pressure at nighttime (62359,62416,62441,62826,108947). Some evidence shows that immediate-release melatonin does not have this effect (62826).

Some evidence also suggests that melatonin seems to slightly reduce blood pressure in patients without hypertension, but to a lesser degree (103689). However, a very small clinical study in healthy young adults consuming a high sodium diet (6900 mg daily) shows that taking melatonin 10 mg before bedtime for 10 days decreases nighttime SBP but does not improve nighttime DBP, daytime SBP or DBP, 24-hour SBP or DBP, or nocturnal dipping of SBP or DBP when compared with placebo (112442).

Insomnia. In patents with insomnia, oral melatonin seems to shorten the time it takes to fall asleep by about 7-12 minutes, although the effect on the amount of time asleep is inconclusive. Melatonin is more likely to be beneficial in older adults or people with certain comorbidities.

Details: Short-term melatonin treatment appears to modestly reduce the time it takes to fall asleep (sleep latency) in otherwise healthy adults with insomnia. This reduction in sleep latency appears to amount to only about 7-12 minutes and might not be considered clinically relevant. Melatonin does not appear to improve sleep efficiency and may only increase total sleep time by about 8 minutes (15005,88290). Despite lack of substantial improvements in objective measures, some patients report minor improvement in subjective feelings of sleep quality (1070,1083,12226,88290).

In children aged 6-12 years with insomnia due to delayed onset of sleep, melatonin 5 mg or 0.05-0.15 mg/kg at bedtime for up to 4 weeks seems to shorten the time that it takes to fall asleep and increases the duration of sleep (9708,62345,62770). More evidence is needed on the long-term effects of melatonin for insomnia.

Some evidence shows that taking oral melatonin might be most beneficial for insomnia in elderly patients who could be melatonin deficient (1072,1729,1738,1754,7081,15005,62357,62465,62472,62613)(62776,62789). Taking sustained-release melatonin preparations 2 mg daily seems to improve sleep maintenance and sleep quality in elderly individuals (1738,1754,62465,62472,62613,62776), while immediate-release preparations seem to decrease sleep latency (1738,63041). In these clinical trials, controlled-release, fast-release, or slow-release melatonin 2-3 mg before bedtime for up to 29 weeks has been used (1072,1738,1754,7081,62357,62465,62472,62613,62776,62789). However, using a melatonin patch placed on the gums does not improve sleep parameters in elderly patients with insomnia (63062).

Some research shows that taking melatonin when taken either alone or in combination with other sleep aids such as bright-light treatment seems to be beneficial for insomnia in patients with certain comorbid conditions. Taking melatonin 2-12 mg for up to 4 weeks has been used to improve insomnia in patients with depression (1053,1729), schizophrenia (8245,62452), bipolar disorder (62140), asthma (62375), cystic fibrosis (62708), hospitalization (9709,106295), and insomnia termed "ICU syndrome", which refers to sleep disturbances while in the intensive care unit (8240). Insomnia is also improved in children aged 3-12 years with epilepsy taking 6-9 mg of melatonin before bedtime for 4 weeks (62394,99342) and quality of sleep is modestly improved in adults with epilepsy taking 3 mg before bedtime for 8 weeks (110299). There is also evidence that melatonin can improve total sleep time and sleep-onset latency in children with tuberous sclerosis (1747), autism spectrum disorders (1056,62811,88286,96318,106293,110290), developmental disabilities (9707), and neurodevelopmental disorders (21819,62143,88283). It also appears to decrease sleep latency and increase sleep time in adults and children with intellectual disabilities, with or without epilepsy (62373,62561). While some evidence shows that fast-release melatonin is more effective for improving the time to fall asleep in children with sleep-wake cycle disturbances and neurodevelopmental disabilities, it is unclear if controlled-release melatonin provides any additional benefits in this population (62143,95746).

However, there is conflicting evidence regarding the effects of melatonin in patients with insomnia and comorbid conditions such as Alzheimer disease or dementia. Some clinical research shows that taking melatonin 3-5 mg before bedtime for up to 10 weeks, either alone or in combination with bright-light treatment, improves impaired sleep related to Alzheimer disease or dementia (1729,62474,63059). But not all research agrees. Meta-analyses of several clinical studies show that taking melatonin 3-10 mg daily improves subjective sleep quality, but not objective outcomes such as number of awakenings at night and sleep efficiency in these patients. Also, immediate-release melatonin 2.5-10 mg or prolonged-release melatonin 1.5-2.5 mg for 10 days to 24 weeks shows inconsistent effects on total sleep time at night in patients with Alzheimer disease (96319,96320).

There is also mixed evidence regarding the effects of melatonin in patients with Parkinson disease. Some subjective outcomes such as sleep quality seem to improve. However, the improvement might not be clinically significant, and objective outcomes such as sleep efficiency and total sleep time at night do not seem to improve (62403,62454,62829,96320).

Melatonin has also been evaluated in postoperative patients and patients with traumatic brain injury (TBI). Taking melatonin before bed does not improve sleep quality soon after tracheostomy, laparoscopic cholecystectomy, or total knee arthroplasty (62439,62552,99343,100255) or 2-6 weeks after total joint arthroplasty (106305). In adults with TBI, one clinical study shows that taking prolonged-release melatonin (Circadin, Sigma Pharmaceuticals) 2 mg two hours prior to bedtime for 4 weeks improves sleep quality, efficiency, and fatigue when compared with placebo. However, melatonin did not improve sleep onset latency or daytime sleepiness. There appears to be no association between TBI severity and the effect of treatment (96317).

There is mixed evidence regarding the effect of melatonin in patients undergoing hemodialysis. Some evidence shows that taking melatonin (Pharma Nord) 3 mg before bed for 6 weeks reduces time needed to fall asleep, improves sleep efficiency, and increases actual sleep time when compared with placebo (62521). Other clinical research in patients undergoing hemodialysis shows that taking immediate-release melatonin 3 mg (Puritans Pride, USA) for 3 months modestly improves various sleep measures when compared with placebo. After treatment, 63.0% of those taking melatonin had no insomnia compared with 7.7% of those taking placebo (110291). However, other evidence shows that taking immediate-release melatonin (Pharma Nord) 3 mg nightly for 12 months does not improve quality of life or sleep efficiency in these patients, indicating that melatonin may not improve sleep long-term (89501).

Finally, limited evidence shows that melatonin does not improve insomnia in patients with substance use disorders (97441).

Jet lag. Taking oral melatonin 2-3 mg daily while travelling seems to improve alertness and reduce daytime sleepiness in people with jet lag. It is unclear if it improves sleep efficiency in this population. Higher doses might have a hypnotic effect.

Details: Most research shows that melatonin can modestly improve certain symptoms of jet lag such as alertness and psychomotor performance. Melatonin also seems to improve, to a lesser extent, other jet lag symptoms such as daytime sleepiness and fatigue (12226). Melatonin might not be effective for decreasing the time to fall asleep (sleep latency) or sleep efficiency in patients with jet lag (6496,14283), although some research shows a beneficial effect of melatonin on these outcomes (62364).

Doses between 0.5-5 mg appear to be equally effective. Although doses of up to 8 mg have been used, doses greater than 5 mg do not seem to be more effective and seem to produce a greater hypnotic effect. Travelers traveling eastward through five or more time zones may find 2-3 mg of melatonin, either slow-release or fast-release, to be useful when taken at local bedtime on the day of arrival and for 2-5 nights thereafter. Taking melatonin in advance of travel does not help prevent jet lag. The usefulness of melatonin for westward travel or over fewer time zones is less clear, although some evidence suggests that slow-release formulations are less effective than fast-release preparations (1049,1077,1079,1085,1722,8273,9181,9750,62706).

Migraine headache. Oral melatonin 3-4 mg seems to prevent migraines when used prophylactically. It is unclear if oral melatonin is beneficial for treating migraine.

Details: Melatonin production might be altered in people with migraine headache (6712,96316). Meta-analyses and individual clinical studies in adults have shown that taking melatonin modestly reduces migraine severity, duration, and frequency, and increases the likelihood of a 50% reduction in the baseline frequency of migraine, when compared with placebo or baseline. Immediate- or prolonged-release melatonin (occasionally as Circadin, Sigma Pharmaceuticals) in doses of 3-4 mg each evening for up to 6 months have been used in these studies (12149,96316,97438,103486,110286). Meta-analyses have included two or three individual clinical trials (103486,110286). One meta-analysis shows that taking melatonin reduces the frequency of migraine days by about 1.7 (103486). An additional meta-analysis in adults with migraines shows that taking melatonin modestly reduces the use of analgesic medications from baseline, when compared with placebo (110286). In contrast, other clinical research shows that taking extended-release melatonin (Circadin, Neurim Pharmaceuticals Ltd.) 2 mg nightly for 8 weeks does not reduce migraine attack frequency when compared with placebo (62784).

Some clinical research also shows that melatonin is as effective as standard treatment for migraine prevention. Some research shows that taking melatonin 3 mg daily for 12 weeks is as effective as amitriptyline 25 mg in reducing migraine frequency, intensity, and duration, as well as reducing analgesic use (96316). A meta-analysis of two clinical trials shows that taking melatonin 3 mg each evening for 8-12 weeks is as effective as standard treatment; however, only one study each compared melatonin with amitriptyline (96316) and valproate (110286). More research comparing melatonin with standard treatments is needed.

Melatonin has also been investigated in children. Preliminary clinical research in children 5-15 years of age with migraine headache shows that taking melatonin 0.3 mg/kg daily for 90 days reduces migraine frequency, severity, and duration, and decreases analgesic use when compared to baseline (97446).

Some research also suggests that melatonin might help to TREAT migraine headache in children and adolescents aged 9-17 years. Preliminary clinical research shows that taking melatonin 1-8 mg reduces pain by a small amount 2-4 hours later. The higher doses of 2 mg for children weighing less than 40 kg and 8 mg for children weighing at least 40

kg seemed to have the greatest benefit (103487). This study is limited by the lack of a comparator group and a very high drop-out rate.

Pre-procedural anxiety. Most research shows that oral or sublingual melatonin reduces preoperative anxiety in adults. The benefit in children is unclear.

Details: A meta-analysis of 18 clinical studies in adults shows that taking oral or sublingual melatonin 3-10 mg or 0.05-0.4 mg/kg 20-120 minutes prior to surgery reduces preoperative anxiety by an average of 12 points on a 100-point visual analogue scale when compared with placebo. It also reduces postoperative anxiety by about 5 points when compared with placebo. Furthermore, a meta-analysis of 7 small clinical trials suggests that melatonin is comparable to benzodiazepines such as midazolam, oxazepam, or alprazolam for reducing preoperative anxiety (105005). In some cases, melatonin might also be preferable to benzodiazepines because it does not cause anterograde amnesia, respiratory depression, or impairment of cognitive and psychomotor skills (88299,99337).

However, research in children is conflicting. One small clinical study in children aged 2-8 years preparing to undergo outpatient elective surgery shows that taking melatonin 0.05-0.4 mg/kg 45 minutes before anesthesia is less effective than midazolam 0.5 mg/kg for reducing anxiety during separation from parents and when putting on the anesthesia mask (62601). In contrast, another small clinical study in children aged 2-5 years undergoing minor elective surgery shows that taking oral melatonin 0.25-0.5 mg/kg 1 hour before anesthesia is similar to midazolam 0.25-0.5 mg/kg for reducing anxiety when separating from parents and when putting on the anesthesia mask (62399). A third study in children aged 3-8 years found no differences between melatonin 0.3 mg/kg, midazolam 0.3 mg/kg, and placebo for reducing preoperative anxiety (106292).

Pre-procedural sedation. Oral melatonin might reduce the sedative dose required to achieve adequate sedation in children. It is unclear if oral melatonin is beneficial for this purpose in adults.

Details: A clinical study in children aged 5-14 years undergoing surgery shows that oral melatonin 0.5 mg/kg reduces the propofol dose required for adequate sedation by 0.77 mg/kg when compared with midazolam 0.5 mg/kg (97444). However, taking melatonin 0.5 mg/kg 45 minutes before surgery is less effective than intranasal dexmedetomidine 2 mg/kg for successful mask acceptance and parental separation (109701). A meta-analysis of clinical and observational studies in children undergoing non-operative procedures, such as electroencephalogram (EEG) and magnetic resonance imaging (MRI), suggests that enteral or parenteral melatonin is no better for adequate sedation than sleep deprivation or chloral hydrate (105884). This finding is limited by imprecision, inconsistency, and a high risk of bias.

A small clinical study in adults undergoing total abdominal hysterectomy shows that taking extended-release melatonin 5 mg, 90 minutes before surgery, decreases the use of midazolam for sedation during surgery when compared with placebo (108945). However, the validity of this finding is unclear, as 0% of patients in the melatonin group required midazolam, compared with 100% of patients in the placebo group. In adults undergoing lower extremity orthopedic surgery with spinal anesthesia, a small study shows that giving melatonin 10 mg orally the night before surgery, followed by 10 mg 2 hours prior to surgery, increases the sedation score when compared with placebo (108951).

Sunburn. Most research shows that topical melatonin seems to protect against erythema from ultraviolet (UV) light exposure.

Details: When applied prior to UV light exposure, a gel containing melatonin 0.05% to 2.5% seems to significantly decrease erythema (1066,1768,1769). In one study, topically applied melatonin in combination with vitamin E 2% and/or vitamin C 5%, was modestly photoprotective when used prior to UV exposure, but had no effect when used during or after UV exposure (4713,4714). Other preliminary clinical research shows that applying a cream containing melatonin 12.5% prior to sun exposure reduces erythema in adults with high sun reactivity, but not in those with mild to moderate sun reactivity. Creams containing melatonin 0.5% or 2.5% did not reduce erythema in

any skin types when compared with placebo (97443). The differences in these findings may be related to the different topical formulations used.

Temporomandibular disorders (TMD). Oral melatonin seems to moderately reduce pain in females with TMD.

Details: Clinical research shows that taking melatonin 5 mg at bedtime for 4 weeks reduces pain by 44% and increases the ability to withstand pain by 39% when compared with placebo in females with TMD. This results in reduced analgesic use and improved sleep quality (89508).

Thrombocytopenia. Oral melatonin seems to improve and prevent thrombocytopenia associated with cancer, cancer treatment, and other disorders.

Details: Clinical research shows that taking melatonin can improve thrombocytopenia associated with cancer, cancer treatment, and other disorders. Melatonin 20-40 mg daily beginning up to 7 days before chemotherapy and continuing for up to four chemotherapy cycles or until disease progression has been used (1694,1695,1696,1697,2564,8268).

POSSIBLY INEFFECTIVE

Athletic performance. Most research suggests that oral melatonin does not improve athletic performance or physical strength.

Details: Taking melatonin 6 mg one hour prior to heavy resistance exercise does not seem to improve maximal strength or maximal jumping ability (62424). Also, taking melatonin 5 mg at night does not appear to improve exercise performance the following morning in healthy athletes (62179). Furthermore, taking melatonin 5 mg 15 minutes prior to exercise does not appear to impact endurance during a cycling trial when compared with placebo (99338). However, some research disagrees. One small clinical trial in professional soccer players shows that taking melatonin 5 mg daily during a six-day training schedule modestly attenuates deterioration in physical performance, such as jumping, agility, and sprints, when compared with placebo (109700).

Cachexia. Oral melatonin does not seem to improve appetite or body composition in patients with cachexia and cancer.

Details: Clinical research in cachectic patients with advanced lung or gastrointestinal cancers shows that taking melatonin 20 mg each evening for 28 days does not improve appetite, body weight, or body composition when compared with placebo (88287).

Cancer-related fatigue. Oral melatonin does not seem to improve fatigue in patients with cancer.

Details: A meta-analysis of five clinical trials shows that taking melatonin does not reduce fatigue in patients with cancer (109697). Most studies used melatonin 20 mg daily, with a duration of 7 days to one year (99344,109697). Although most studies included in the analysis were small, one contained over 700 patients and lasted one year. However, some research disagrees. Preliminary clinical research in adults with breast cancer shows that taking melatonin 18 mg orally daily for 2 years moderately improves fatigue scores when compared with placebo (112054).

Cancer-related pain. Oral melatonin does not seem to improve pain in patients with cancer.

Details: A meta-analysis of five clinical trials shows that taking melatonin does not reduce pain in patients with cancer (109697). Most studies used melatonin 20 mg daily, with a duration of 10 days to one year (109697). Although most studies included in the analysis were small, one contained over 700 patients and lasted one year.

Critical illness (trauma). Oral melatonin does not seem to be beneficial for reducing hospital stay in critically ill patients.

Details: A meta-analysis of clinical research in critically ill patients shows that taking melatonin does not reduce the length of stay in the ICU or the hospital, or affect mortality or sleep quality, when compared with placebo (109696). One additional small clinical study shows that receiving melatonin 3 mg through a nasogastric tube once at 9 pm, followed by a 0.5 mg hourly maintenance dose for 6 hours during the overnight period, does not improve sleep when compared with placebo in patients in the ICU that are being weaned off sedatives and mechanical ventilation (104997).

Dementia. Oral melatonin does not seem to improve behavior or cognition in patients with dementia. However, it might reduce evening confusion (sundowning).

Details: Most clinical research shows that taking melatonin does not improve cognition or behavioral or affective symptoms in patients with probable Alzheimer disease or other forms of dementia (62421,62530,96319). However, some research shows that taking melatonin 2.5-3 mg before bedtime for up to 10 weeks reduces sundowning, which is the confusion and restlessness experienced by some dementia patients in the evening (62788).

Infertility. Oral melatonin does not seem to increase fertility in females undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).

Details: Some clinical research shows that taking melatonin does not improve fertility rate or clinical pregnancy rate in adults undergoing IVF, although oocyte and embryo quality might be improved (62775,62818,62819,88297,89512). Also, results from meta-analyses of clinical research show that melatonin does not improve clinical pregnancy rate, total number of oocytes retrieved, or the rate of miscarriage, although it seems to increase the number of mature oocytes (89505,106304). Most studies have used single doses of 3 mg daily which may not be adequate (106304).

Melatonin has also been evaluated in adults undergoing ICSI. Although one study shows that taking melatonin improves the fertilization rate, the clinical pregnancy rate was not evaluated (88297). Other research in females taking melatonin and undergoing ICSI does not show an increase in clinical pregnancy rate (97445).

Shift work disorder. Oral melatonin does not seem to improve sleep in individuals doing shift work.

Details: Taking melatonin orally doesn't seem to significantly improve the time it takes to fall asleep (sleep latency), sleep efficiency, or adjustment to rotating shift work. However, slight increases in total sleep time during the day or overall sleep quality may occur (1052,1054,1721,14283,62200,62401,62462,62942).

LIKELY INEFFECTIVE

Benzodiazepine withdrawal. Oral melatonin does not facilitate benzodiazepine discontinuation in patients with insomnia.

Details: Although some small studies show benefit (349,1751), results from larger clinical studies and a meta-analysis of clinical research show that taking melatonin 2-5 mg before bedtime for up to 6 weeks does not help facilitate benzodiazepine discontinuation in patients with insomnia (62464,62467,63075,88295,96321,96323).

Depression. Most research shows that oral melatonin does not reduce symptoms of depression or prevent depression. In some patients, taking melatonin might make symptoms worse.

Details: Most research shows that taking melatonin 5-10 mg daily before bedtime for 4-12 weeks, alone or with fluoxetine, does not improve depression symptoms in patients with rapid cycling bipolar disorder (1766) or major depressive disorder (MDD) (1053,62746,96326). However, some research shows that taking slow-release melatonin 3

mg in combination with immediate-release buspirone 15 mg daily for 6 weeks is more effective at improving depression severity and depression symptoms than placebo or buspirone alone in patients with MDD (88289). However, buspirone is not commonly used for the management of depression. Also, there is some concern that oral melatonin may worsen symptoms in some patients with unipolar or bipolar depression (1764).

Evidence regarding the effects of melatonin for preventing depression is unclear. One clinical study shows that taking melatonin 6 mg daily for 12 weeks reduces the percentage of breast cancer patients who develop depression following a lumpectomy or mastectomy by about 75% when compared with placebo when an intention to treat analysis is used. However, when only patients who took all of the doses are considered, melatonin does not appear to have an effect (89511). Also, a meta-analysis of clinical research including two studies in patients with irritable bowel syndrome (IBS) who were at risk for depression shows that melatonin does not prevent depression when compared with placebo (96326).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Acute kidney injury (AKI). It is unclear if oral melatonin is beneficial for acute kidney injury.

Details: A meta-analysis of randomized clinical trials in adults with drug-induced acute kidney injury shows that taking melatonin 3-30 mg orally daily for up to 6 days modestly improves glomerular filtration rate, but not serum creatinine or incidence of acute kidney injury, when compared with placebo (111463).

Age-related macular degeneration (AMD). It is unclear if oral melatonin prevents vision loss in patients with AMD.

Details: Preliminary clinical research shows that taking melatonin 3 mg daily for 3-6 months may delay the loss of clear vision in individuals with AMD when compared with baseline (62419). The validity of this finding is limited by the lack of a comparator group.

Atopic dermatitis (eczema). Oral melatonin might improve some symptoms of atopic dermatitis. However, it is unclear if it improves sleep in this population.

Details: Preliminary clinical research in children ages 1-18 years with atopic dermatitis and sleep disturbance shows that taking melatonin 3 mg daily for 4 weeks modestly reduces the overall atopic dermatitis symptom score by 19% when compared with placebo (97439). In another clinical study in children with atopic dermatitis, taking melatonin 6 mg daily 1 hour before bedtime for 6 weeks seems to improve disease severity and sleep quality when compared with placebo (99347). It is unclear whether melatonin improves sleep latency in this population, as conflicting results exist (97439,99347).

Attention deficit-hyperactivity disorder (ADHD). It is unclear if oral melatonin is beneficial for ADHD.

Details: Some small clinical studies in children with ADHD who are taking stimulants show that melatonin 3-5 mg daily for up to 3 months might reduce insomnia when compared with placebo (9980,15034). However, improved sleep related to melatonin treatment does not seem to result in fewer symptoms of ADHD (15034).

Autism spectrum disorder. It is unclear if oral melatonin is beneficial for this condition.

Details: One clinical trial in children aged 6-15 years with autism spectrum disorder shows that taking melatonin (Nobelpharma Co., Ltd) 1 mg or 4 mg before bedtime does not affect behavior when compared with placebo. However, this study was designed to evaluate sleep outcomes, not behavior, as a primary endpoint (106293). Also, a secondary analysis of results from a clinical trial in children with autism spectrum disorder shows that taking prolonged-release melatonin mini-tablets (PedPRM) 2-5 mg nightly for 13 weeks improves externalizing behavior in 26% more patients when compared with those taking placebo. There was no difference between groups in behaviors

such as hyperactivity, inattention, emotional behavior, and relationships with peers (101256). The validity of these findings is limited by the secondary nature of the analysis, which was not designed to evaluate these outcomes.

Benign prostatic hyperplasia (BPH). It is unclear if oral melatonin is beneficial for BPH.

Details: One very small clinical study shows that taking controlled-release melatonin 2 mg nightly for 4 weeks reduces excessive urination at night in some men with BPH when compared with placebo. However, it is unclear if this improvement is clinically significant (62360).

Bipolar disorder. It is unclear if oral melatonin is beneficial for this condition.

Details: Preliminary clinical research shows that taking melatonin 3 mg at bedtime for 30 days increases sleep duration and reduces mania severity when compared to baseline in patients with bipolar disorder and treatment-resistant insomnia (62140). However, other research shows that melatonin is not beneficial in patients with bipolar disorder when compared with placebo. Taking melatonin 3-10 mg daily before bedtime for 3-12 weeks does not seem to improve mania or other symptoms when compared with placebo (1766,103694). Also, taking a specific brand of slow-release melatonin (Cronocaps, Productos Medix) 5 mg each evening for 8 weeks may attenuate the increase in blood pressure and fat mass that is associated with use of second-generation antipsychotics, but it does not appear to improve mania or depression in patients with bipolar disorder (88300). There is also some concern that oral melatonin may worsen symptoms in some patients with bipolar depression (1764).

Bronchopulmonary dysplasia. It is unclear if oral melatonin reduces the risk of bronchopulmonary dysplasia (BPD) in premature infants.

Details: A small clinical study in premature infants with respiratory distress syndrome who received surfactant shows that giving melatonin 3 mg daily for 7 days reduces the incidence of BPD to 45%, compared with 60% in those not receiving melatonin. Melatonin also reduced the duration of hospital stay, need for mechanical ventilation, and mortality (108948).

Chronic fatigue syndrome (CFS). It is unclear if oral melatonin is beneficial for patients with CFS.

Details: Many patients with CFS have circadian rhythm disturbances. Some very small clinical studies have evaluated the use of melatonin for addressing these disturbances. One study shows that taking melatonin 5 mg in the evening for 12 weeks might improve some measures of fatigue, concentration, motivation, and activity when compared with baseline (14437). However, other preliminary clinical research shows that taking the same dose of melatonin does not improve CFS symptoms when compared with placebo (9705).

Melatonin has also been studied in combination with zinc. In patients with CFS, taking melatonin 1 mg plus zinc 10 mg before bedtime for 16 weeks modestly reduces self-reported levels of physical fatigue, but not self-reported cognitive or psychological symptoms, mood, sleep quality, or quality of life (QOL) measures, when compared with placebo. However, some measures of sleep quality and QOL worsened within 4 weeks of melatonin discontinuation, suggesting that there may have been a modest benefit (106241). It is unclear whether any benefit is related to melatonin, zinc, or the combination. Also, all patients in this study were White females, limiting the generalizability of the results.

Chronic obstructive pulmonary disease (COPD). It is unclear if oral melatonin is beneficial for COPD.

Details: Some clinical research shows that taking melatonin 3 mg daily for 3 months improves shortness of breath in patients with COPD when compared with placebo, although melatonin does not seem to improve lung function or exercise capacity (62854).

Cluster headache. It is unclear if oral melatonin prevents cluster headaches.

Details: A very small clinical study in adults with cluster headaches shows that taking melatonin orally 10 mg every evening for 14 days might reduce the frequency of episodic cluster headaches when compared with placebo (1127). However, 2 mg at bedtime does not seem to be effective (9702).

Cognitive impairment. Oral melatonin has only been evaluated in combination with other ingredients; its effect when used alone is unclear.

Details: Clinical research in adults 70 years and older with mild cognitive impairment shows that taking two capsules containing melatonin 5 mg, docosahexaenoic acid (DHA) 720 mg, eicosapentaenoic acid (EPA) 286 mg, vitamin E 16 mg, soy phospholipids 160 mg, and L-tryptophan 95 mg (IBSA Farmaceutici) before bedtime for 12 weeks modestly improves cognitive function and sensitivity to smells when compared with placebo. The observed improvement on the mini-mental state examination (MMSE) scale falls below the score generally considered to be indicative of true changes in cognitive function, and may not be clinically significant. Also, it is not known if any potential benefit is due to melatonin, other ingredients, or the combination (62847).

Colorectal cancer. It is unclear if oral melatonin is beneficial for colorectal cancer prevention.

Details: Population research suggests that any history of melatonin use is associated with an approximate 20% reduction in the incidence of colorectal cancer, especially rectal cancer, in individuals aged 60 years and older (106291).

Contraception. Although there has been interest in using oral melatonin for contraception, there is insufficient reliable information about the clinical effects of melatonin for this use.

Coronary artery bypass graft (CABG) surgery. It is unclear if oral melatonin is beneficial for recovery from CABG surgery.

Details: Clinical research shows that taking melatonin perioperatively during CABG surgery reduces the length of stay in the ICU by about 0.5 days and modestly reduces levels of creatine kinase-MB when compared with placebo. However, there was no effect on the length of hospital stay or levels of cardiac troponin-I, C-reactive protein, or erythrocyte sedimentation rate. Oral melatonin 3 mg was provided the night before and morning of surgery, as well as at bedtime for 3 days after surgery (109699).

Coronavirus disease 2019 (COVID-19). Preliminary clinical studies suggest that oral melatonin may reduce disease severity in patients with COVID-19, although some conflicting findings exist.

Details: A meta-analysis of mainly small and preliminary randomized clinical trials in patients with COVID-19 shows that taking melatonin improves clinical outcomes when compared with placebo. However, the clinical outcomes differed between individual trials, and included specific symptoms, hospital discharge, removal from quarantine, and survival. Dosing also varied, with doses of 2-24 mg daily in 1-4 divided doses for 6-14 days. There was no effect of melatonin on C-reactive protein levels or oxygen saturation (109695).

Individual clinical trials have been conducted in hospitalized and/or non-hospitalized patients with mild to severe COVID-19. One clinical trial in outpatients with mild to moderate COVID-19 shows that taking melatonin 10 mg daily modestly reduces time to symptom resolution and quality of life improvement when compared with placebo (109462). However, it is unclear if any beneficial effects are clinically meaningful. In patients hospitalized and receiving standard care for mild to moderate COVID-19, a small clinical trial shows that taking melatonin 3 mg three times daily for 14 days reduces the mean time to hospital discharge by approximately 3.5 days when compared with placebo. Also, persistent symptoms of cough, dyspnea, and fatigue after 14 days occurred in only 0% to 8% of patients taking melatonin, compared with 15% to 30% of those taking placebo. However, there was no difference in the number of patients with other symptoms, including fever, myalgia, chill, and headache (106300). The validity of this study is limited by its high attrition rate. Another small clinical trial in patients hospitalized with COVID-19 shows that taking

melatonin (Norm Life Vanatonin Melatonin) 3 mg nightly for 7 days does not reduce symptoms or prevent ICU admission or death when compared with standard care alone (106295). The low dose and short duration of use in this study might have played a role in the lack of benefit.

Melatonin has also been evaluated in patients hospitalized for severe COVID-19. One large single-center preliminary clinical trial shows that taking melatonin 10 mg daily reduces the incidence of thrombosis at day 17 and the incidence of sepsis at day 11 when compared with standard care alone. Death occurred in approximately 17% of patients taking placebo, compared with 1% of those taking melatonin (106289). Another preliminary clinical trial in patients in the ICU for severe COVID-19 shows that taking melatonin (Danna Pharmaceutical Company, Iran) 5 mg twice daily for 7 days results in mortality and invasive mechanical ventilation rates of 67% and 51.4%, respectively, compared with 94% and 70.9% in patients given standard care only. There were also modest improvements in the time to improvement of clinical status and lengths of stay in the hospital and ICU (110297). The validity of these studies is limited by a lack of blinding.

Delirium. It is unclear if oral melatonin is beneficial for preventing delirium in hospitalized patients; the available research is conflicting.

Details: Research is conflicting on whether melatonin reduces the incidence of delirium. One meta-analysis of 10 clinical trials shows that melatonin reduces the incidence of delirium in critically ill patients in the intensive care unit (ICU) by 21% when compared with a control, usually placebo (109696). However, other meta-analyses of 14 small clinical and observational studies of hospitalized patients show that taking melatonin does not reduce the incidence of delirium when compared with control (105003,112440). Melatonin might be less beneficial in non-acute medical patients when compared with postoperative patients or those in the ICU (105003).

There is also a lack of consensus within the available research on whether melatonin reduces the duration of delirium in hospitalized patients. One meta-analysis of 10 clinical trials shows that melatonin does not reduce the duration of delirium (109696). However, a meta-analysis of 2 small, randomized controlled trials shows that taking melatonin 3-5 mg daily for 5 or more days reduces the duration of delirium by approximately 2 days when compared with placebo (112051). This analysis is limited by substantial heterogeneity and a lack of dose-response evaluation. Most studies in these analyses have used doses of 0.5-10 mg daily for up to 14 days, although one study used a very high single dose of 50 mg/kg (105003,105891,107809,108949,109696,112051).

Some research suggests that melatonin may be beneficial for patients undergoing cardiac procedures. A subgroup analysis of one meta-analysis including 3 small studies suggests that melatonin reduces the incidence of delirium in patients in cardiovascular care units, but not in the general ICU population (112440). Two large clinical studies in the meta-analysis suggest that, in older patients admitted to the ICU after acute heart failure or percutaneous coronary intervention (PCI), taking melatonin 3 mg once daily for up to 7 days is associated with a 27% incidence of delirium, compared with a 37% to 40% incidence with placebo (107809,108949). Additionally, a small clinical study in patients undergoing coronary artery bypass graft (CABG) surgery suggests that taking prolonged-release melatonin (Webber Naturals) 3 mg twice before surgery and twice after surgery reduces the occurrence of delirium over the next 48 hours when compared with placebo (105891). The validity of this study is limited by a high risk of bias due to insufficient blinding and incomplete outcome data.

Additionally, a small clinical study shows that receiving melatonin 3 mg through a nasogastric tube once at 9 pm, followed by a 0.5 mg hourly maintenance dose for 6 hours during the overnight period, does not reduce delirium or improve sleep when compared with placebo in patients in the ICU that are being weaned off sedatives and mechanical ventilation (104997).

Diabetes. Most research shows that oral melatonin is beneficial for improving glycemic control. However, it is unclear if oral melatonin is beneficial in patients with type 2 diabetes.

Details: Most research on the use of melatonin for glycemic control has been conducted in mixed populations, such as those with schizophrenia, metabolic syndrome, nonalcoholic steatohepatitis (NASH), or perimenopause (103490,106294,106298). Two recent meta-analyses of clinical research in these populations show that taking melatonin modestly reduces fasting glucose and insulin, insulin resistance, and glycated hemoglobin (HbA1c), and improves insulin sensitivity (106294,106298). The most common doses of melatonin used were 3 -10 mg for 8-24 weeks; however, 10 mg may be more effective (106294,106298). This contrasts with an earlier meta-analysis showing only modest beneficial effects of melatonin on fasting glucose levels and insulin sensitivity (103490).

Research on the use of melatonin in patients with type 2 diabetes is limited. One small clinical trial in patients with type 2 diabetes show that taking melatonin (NatureMade) 6 mg daily for 8 weeks does not improve glycemic control (104368). However, this trial may have been underpowered to detect a difference. Another very small study in adults with type 2 diabetes shows that taking melatonin 3 mg daily before bed for 7 days increases absolute glucose level at breakfast on day 7 and the glycemic difference between post-dinner on day 6 and pre-breakfast on day 7 but does not change most measures of glycemic variability including mean glucose levels, pre-prandial glucose levels, and post-prandial glucose levels compared with placebo (112441).

Diabetic neuropathy. It is unclear if oral melatonin is beneficial for improving pain in patients with diabetic neuropathy.

Details: A clinical study in patients with painful diabetic neuropathy living in Iran shows that taking melatonin 3 mg nightly for 1 week and then 6 mg nightly for 7 weeks, in conjunction with pregabalin 150 mg daily seems to reduce pain and sleep interference to a greater degree than placebo and pregabalin (105895).

Dry mouth. It is unclear if oral melatonin is beneficial for dry mouth caused by radiation treatment.

Details: A small clinical study in patients with head and neck cancer undergoing chemoradiation shows that taking melatonin 20 mg orally at bedtime and using 10 mL of melatonin 0.2% oral gargle 15 minutes before each radiation session does not delay the onset or reduce the incidence of grade 2 dry mouth when compared with placebo. However, the incidence of grade 3 dry mouth is delayed by approximately 16 days (96314).

Dysmenorrhea. It is unclear if oral melatonin is beneficial for dysmenorrhea.

Details: A small clinical trial shows that taking melatonin 10 mg nightly before bed during the week of menstruation has a statistically significant effect on pain severity when compared with placebo. However, the pain reduction was not considered clinically significant (106301).

Dyspepsia. It is unclear if oral melatonin is beneficial for dyspepsia in adults.

Details: Preliminary clinical research shows that taking melatonin 5 mg nightly for 12 weeks improves dyspeptic symptoms in individuals with functional dyspepsia. However, the benefit seems to be decreased in patients with prior Helicobacter pylori infection (62456).

Endotracheal intubation-associated adverse effects. It is unclear if oral melatonin is beneficial for endotracheal intubation-related hemodynamic effects.

Details: Clinical research shows that taking immediate-release melatonin (Healthy Hey Nutrition) 6 mg, 2 hours prior to the induction of anesthesia, is as effective as clonidine 0.2 mg for attenuating the hemodynamic response to laryngoscopy and tracheal intubation (103483). It is not known if melatonin prevents other adverse effects associated with endotracheal intubation.

Endometriosis. It is unclear if oral melatonin reduces endometriosis-related pain.

Details: Preliminary clinical research shows that taking melatonin 10 mg daily for 8 weeks reduces pain by about 39% and analgesic use by about 46%, as well as pain during menstruation, intercourse, and evacuation, when compared with placebo in adults with endometriosis (89503). Other clinical research in adults with endometriosis shows that taking melatonin 20 mg orally daily does not improve pain scores or reduce pain during intercourse, urination, or defecation when compared with placebo (111464). However, the study may have been inadequately powered to detect a difference between groups.

Epilepsy. It is unclear if oral melatonin is beneficial for epilepsy in children or adults.

Details: There is some low-quality evidence that taking melatonin 3 mg at bedtime for 3 months might reduce the frequency and duration of both nocturnal and daytime seizures in children aged 2-15 years with epilepsy (9699,9745,9746,62785). Also, taking melatonin 1.5 mg before bed for 3 months might reduce the seizure severity in children with epilepsy that is not successfully controlled with other treatment (62754). Furthermore, taking fast-release melatonin 10 mg daily for 3 weeks seems to reduce diurnal seizure frequency in both adults and children aged 9 years and up with intractable epilepsy (88291).

Limited research has also assessed melatonin as an adjunct therapy in adults with seizure disorders. A small clinical study in adults with epilepsy involving generalized onset motor seizures that recurred within the last three days shows that adding melatonin 3 mg before bed to therapy with valproate 20 mg/kg in two divided doses daily for 8 weeks results in 82% of patients having at least a 50% reduction in seizure frequency, compared with only 53% of patients in the group taking valproate and placebo. Adding melatonin may also improve seizure severity (105006). However, other clinical research in adults under valproic acid treatment for idiopathic generalized tonic-clonic seizures alone shows that taking melatonin 3 mg before bed for 8 weeks modestly reduces seizure severity, but not frequency (110299).

Fibromyalgia. It is unclear if oral melatonin is beneficial for this condition.

Details: Preliminary clinical research shows that taking melatonin 3-5 mg daily for up to 60 days may decrease the severity of pain and stiffness, as well as the number of painful joints, in people with fibromyalgia when compared with placebo (9701,62797).

Gastroesophageal reflux disease (GERD). It is unclear if oral melatonin is beneficial for GERD.

Details: Clinical research shows that taking melatonin 3 mg daily at bedtime for 8 weeks may improve symptoms of GERD, including heartburn and epigastric pain. However, taking omeprazole 20 mg twice daily seems to be more effective (62723).

Helicobacter pylori. It is unclear if oral melatonin is beneficial for Helicobacter pylori eradication.

Details: One very small clinical study shows that taking melatonin 5 mg twice daily in combination with omeprazole 20 mg twice daily for 21 days improves ulcer healing rates when compared with omeprazole alone in individuals with H. pylori-associated gastroduodenal ulcers (62803).

Heart failure. It is unclear if oral melatonin is beneficial for heart failure.

Details: A small clinical study in adults with stable NYHA class II or III heart failure with reduced ejection fraction (HFrEF) and a left ventricular ejection fraction (LVEF) below 40%, shows that taking melatonin 10 mg orally every evening for 24 weeks improves a composite score reflecting all-cause mortality, hospitalization for exacerbation, and quality of life when compared with placebo. Melatonin also attenuates an increase in serum B-type natriuretic peptide levels, but does not affect LVEF or left ventricular end-diastolic or end-systolic diameter (108950).

Irritable bowel syndrome (IBS). It is unclear if oral melatonin is beneficial for IBS.

Details: In patients with IBS who also have poor sleep, taking melatonin 3 mg at bedtime for 2 weeks seems to decrease symptoms of IBS-related abdominal pain and increase the rectal pain threshold when compared with placebo. However, taking melatonin does not seem to influence stool frequency or consistency, bloating, mood, sleep, or overall quality of life (13112). In other small clinical studies, taking melatonin 3 mg at bedtime for 8 weeks decreased severity and frequency of pain, reduced bloating, improved bowel habits, decreased extracolonic symptoms such as headache, heartburn and nausea, and improved overall quality of life when compared with placebo (15216,62410). However, other clinical research shows that melatonin does not significantly affect the amount of time needed for food to travel through the colon in patients with IBS (62500). Also, one small clinical study shows that taking melatonin 3 mg in the morning and 5 mg in the evening for 6 months improves abdominal pain, bloating, and bowel habits in 50% to 70% of postmenopausal patients with constipation-predominant IBS when compared with placebo. However, beneficial effects were reduced in patients with diarrhea-predominant IBS (89510). Other clinical research in patients with IBS shows that taking melatonin 6 mg orally daily for 8 weeks improves IBS symptom severity scores, abdominal pain scores, and bloating scores, when compared with placebo. These results were not different between those with or without sleep disorders at baseline (112055). The large number of endpoints, many with inconsistent results, in these studies makes it difficult to draw conclusions.

Ischemia-reperfusion injury. It is unclear if intravenous or intracoronary melatonin is beneficial for ischemia-reperfusion injury.

Details: A meta-analysis of 9 low-quality clinical trials in patients with myocardial ischemia-reperfusion injury shows that giving melatonin in doses of 2-50 mg by intravenous or intracoronary injection within 2.5-3.5 hours of ischemia onset improves left ventricular ejection fraction and reduces the infarct size, but does not improve left ventricular end-diastolic or end-systolic volumes, when compared with control. Also, giving melatonin orally for up to 12 weeks does not improve cardiac function. The patients in this study experienced injury as a result of an ST-elevation myocardial infarction, ischemic heart disease, acute coronary syndrome, or coronary heart disease (108946).

Kidney failure. It is unclear if oral melatonin is beneficial for improving mood and quality of life in patients on hemodialysis.

Details: A small clinical trial in patients undergoing hemodialysis shows that taking immediate-release melatonin 3 mg (Puritans Pride, USA) for 3 months modestly improves depression, anxiety, and quality of life when compared with placebo. After treatment, 73.1% and 57.7% of those taking placebo had severe depression and anxiety, respectively, when compared with 22.2% and 14.8% of those taking melatonin (110291).

Kidney transplant. It is unclear if oral melatonin is beneficial for improving post-transplant kidney function.

Details: A small clinical study in patients that have received kidney transplants shows that taking melatonin 3 mg daily for an average of 25 days does not affect urine volume or kidney function, as measured by the blood urea nitrogen over creatinine (BUN/Cr) ratio, when compared with placebo (103693).

Lung cancer. It is unclear if melatonin is beneficial in patients with early stage non-small cell lung cancer (NSCLC).

Details: A clinical study in patients who have undergone complete surgical resection of early stage NSCLC shows that taking melatonin 20 mg daily for 1 year does not improve 2-5 year disease-free survival, pain, anxiety, fatigue, or quality of life when compared with placebo (105894). The validity of these findings is limited by a high study withdrawal rate.

Melasma. Although there has been interest in using oral melatonin for melasma and other causes of hyperpigmentation, there is insufficient reliable information about the clinical effects of melatonin for these conditions.

Menopausal symptoms. It is unclear if oral melatonin is beneficial for improving symptoms of menopause; evidence is conflicting.

Details: A meta-analysis of 3-5 clinical studies in patients with menopausal symptoms shows that taking melatonin does not seem to improve vasomotor or psychological symptoms, but may modestly improve physical symptoms, when compared with placebo (105897). This analysis is limited due to inconsistent evidence and some risk of bias within the included studies. Studies included in the meta-analysis used melatonin 3 mg daily for 3-12 months alone or in combination with soy isoflavones 80 mg or fluoxetine 20 mg (11806,62840,105897). In contrast, a small study in adults with menopausal symptoms shows that taking melatonin 3 mg daily for 12 weeks improves climacteric symptoms, anxiety, depressive symptoms, sleep quality, and menopausal quality of life and decreases luteinizing hormone and follicle stimulating hormone levels but does not change uterine volume, endometrial thickness, or estradiol levels when compared with placebo (112443).

Metabolic syndrome. It is unclear if oral melatonin is beneficial for this condition.

Details: Preliminary clinical research in adults with metabolic syndrome shows that taking melatonin 5 mg nightly for 2 months reduces systolic and diastolic blood pressure, as well as low-density lipoprotein (LDL) cholesterol levels, when compared to baseline (62795). The validity of these findings is limited by the lack of a comparator group.

Multiple sclerosis (MS). It is unclear if oral melatonin is beneficial for MS.

Details: A small clinical study in patients with relapsing-remitting MS (RRMS) receiving interferon-beta once weekly shows that taking melatonin 3 mg daily for 12 months does not affect relapse rate, disability, brain lesions, fatigue, or depression when compared with placebo (99345). This small study may not have been adequately powered to detect a difference between groups.

Myocardial infarction (MI). The benefits of administering oral or intravenous melatonin immediately after an MI are unclear.

Details: A meta-analysis of 5 small clinical studies in patients after MI shows that oral or intravenous melatonin, used in conjunction with medical reperfusion, is associated with modestly lower troponin levels and modestly higher left ventricular ejection fraction when compared with control (105889). One clinical study included in this analysis that evaluated patients with ST-segment elevation myocardial infarction (STEMI) shows that intravenous administration of melatonin 51.7 mcmol over 60 minutes immediately prior to percutaneous coronary intervention, combined with a bolus intracoronary dose of melatonin 8.6 mcmol administered within 60 seconds after restoration of blood flow to the infarcted artery, does not reduce myocardial infarct size when compared with placebo. However, subgroup analyses suggest that the timing of melatonin administration after symptom onset may alter its effects (96324).

Neonatal encephalopathy. It is unclear if oral or intravenous melatonin is beneficial for neonates with encephalopathy.

Details: A meta-analysis of two small clinical studies in term or late preterm infants with neonatal encephalopathy who are receiving therapeutic hypothermia shows that receiving melatonin 5 mg/kg intravenously daily for 3 days, or 10 mg/kg orally daily for 5 days, does not reduce mortality when compared with hypothermia alone, although a nonsignificant trend towards a reduction was noted (104994). One of those small studies in term infants with neonatal encephalopathy also shows that receiving adjunct oral melatonin treatment results in fewer seizures and less white matter abnormalities when compared with hypothermia alone (99333).

Nocturnal enuresis. It is unclear if oral melatonin is beneficial for reducing nighttime wettings.

Details: Preliminary clinical research shows that taking melatonin 5 mg nightly before bedtime for 3 months does not reduce the number of wet beds when compared with placebo in children with nighttime wettings (nocturnal enuresis) (62824).

Nonalcoholic fatty liver disease (NAFLD). It is unclear if oral melatonin is beneficial for NAFLD.

Details: A meta-analysis of clinical research, as well as individual clinical trials, show that taking melatonin 6-18 mg daily for 4-56 weeks improves some liver indices, but not others (62853,88285,103484,103485). Overall, taking melatonin seems to modestly reduce levels of alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT). However, there is no effect on alanine aminotransferase (ALT) and levels of aspartate aminotransferase (AST) slightly increased (103485). One small clinical study shows that taking melatonin (Nature Made, USA) 6 mg daily for 12 weeks has a small benefit on systolic and diastolic blood pressure, body mass index (BMI), abdominal circumference, and liver enzymes, but not plasma lipid levels, when compared with placebo (103484). Larger studies are needed to determine the effect of melatonin in this population.

Obesity. It is unclear if melatonin is beneficial for improving weight loss.

Details: A meta-analysis of clinical research shows that taking melatonin up to 10 mg daily, usually for 4-24 weeks, modestly reduces body weight when compared with placebo. However, there was no effect on body mass index (BMI) or waist circumference. Also, the studies included in the analysis were not limited to overweight or obese individuals. Populations included those with metabolic syndrome, nonalcoholic steatohepatitis (NASH), schizophrenia, polycystic ovary syndrome (PCOS), and others, as well as postmenopausal adults (106288). A small clinical trial in overweight or obese individuals shows that although taking melatonin 3 mg daily for 12 weeks modestly reduces waist circumference and body fat mass when compared with placebo, there is no effect on body weight or BMI (106290).

Oral mucositis. Most research shows that melatonin does not prevent or reduce the severity of oral mucositis in patients with head and neck cancer receiving radiation and chemotherapy. It is unclear if oral or topical melatonin is beneficial in patients with other types of cancer.

Details: A meta-analysis of seven clinical trials including patients undergoing chemotherapy or radiotherapy shows that melatonin does not reduce the rate of oral mucositis when compared with a control, usually placebo (109697). Although a small clinical study in patients with head and neck cancer undergoing radiation and chemotherapy with cisplatin shows that melatonin delays the onset of severe mucositis by 16 days when compared with placebo (96314), a meta-analysis shows that melatonin does not reduce the rate of oral mucositis in patients with head and neck cancer (109697). A sub-analysis in one meta-analysis suggests that taking melatonin, usually 20 mg daily, reduces the rate of oral mucositis by 53% in patients with cancer types other than head and neck (109697). Most studies investigating the effect of melatonin have used oral melatonin 20 mg at bedtime. However, in one study, 10 mL of melatonin 0.2% oral gargle was also used 15 minutes before radiation (96314). In another, swishing with 10 mL of a melatonin 3% gel mouthwash for 2 minutes and then swallowing, starting 2-3 days before radiotherapy and continuing until 1-4 weeks after the end of radiotherapy, was used (105893).

Melatonin has also been investigated for oral mucositis severity. Although some individual research disagrees (96314), a meta-analysis of three clinical trials shows that melatonin does not reduce the severity of oral mucositis when compared with placebo. However, the form of melatonin provided in these studies was heterogeneous, including oral, gargle, and gel formulations (96314,105893,109697).

Osteopenia. It is unclear if oral melatonin is beneficial for improving bone mineral density.

Details: A small clinical study in postmenopausal adults with osteopenia shows that taking melatonin 3 mg nightly for 1 year increases tibia thickness by 2.2% and volumetric bone mineral density (BMD) in the spine by 3.6%

when compared with placebo. However, the BMD of other skeletal sites was not impacted. Additionally, a 1 mg melatonin dose was not beneficial (99334).

Osteoporosis. Although there has been interest in using oral melatonin for osteoporosis, there is insufficient reliable information about the clinical effects of melatonin for this condition.

Pain (acute). It is unclear if oral melatonin is beneficial for acute pain.

Details: Clinical research in patients undergoing laparoscopic cholecystectomy shows that taking melatonin 6 mg two hours before induction with propofol reduces the number of patients requiring intraoperative fentanyl to 10%, compared with 35% of those taking placebo (106299). Also, preliminary clinical research in preterm infants also given standard treatments shows that oral melatonin (Syrup Trunap, Brio Bliss Life Science Pvt. Ltd) 20 minutes prior to retinopathy of prematurity screening, is not inferior to 24% sucrose for reducing pain (110295). However, the effect of sucrose itself is inconclusive and this study is limited by a lack of blinding. Also, it is unclear if melatonin is beneficial for other causes of acute pain.

Pain (chronic). It is unclear if melatonin is beneficial for most causes of chronic pain.

Details: A meta-analysis of 5 clinical studies shows that taking melatonin 3-12 mg daily for up to 12 weeks modestly reduces chronic pain when compared with placebo (103692). However, it is difficult to draw clinical conclusions from this analysis, as it pools the effects observed in various types of chronic pain, including migraine, burning mouth syndrome, endometriosis, and irritable bowel syndrome (IBS).

Periodontitis. Small clinical studies suggest that oral melatonin may improve some measures of periodontitis severity.

Details: A meta-analysis of 7 small clinical trials in patients with periodontitis treated with subgingival instrumentation to remove calculus and bacterial biofilms shows that adding oral melatonin in doses of 3-10 mg daily improves probing depth, clinical attachment loss, and gingival index when compared with instrumentation alone (108953).

Polycystic ovary syndrome (PCOS). It is unclear if melatonin is beneficial for PCOS.

Details: A prospective cohort study in patients with PCOS has found that taking melatonin (Armonia Fast, Nathura) 2 mg before bedtime for 6 months increases follicle-stimulating hormone and the total number of menstrual cycles from approximately 2.5 to 4 when compared to baseline (96313). The validity of this study is limited by its observational nature and the lack of a comparator group. Additionally, a small clinical study in patients with PCOS shows that taking melatonin 6 mg daily for 8 weeks does not affect insulin levels, fasting blood glucose, lipid levels, or weight, but might modestly reduce testosterone levels, when compared with placebo (105887). This study may have not been adequately powered to detect differences between groups.

Postoperative nausea and vomiting (PONV). It is unclear if melatonin is beneficial for reducing PONV.

Details: A small clinical trial shows that taking melatonin (Nature Made, USA) 3 mg, 5 mg, or 10 mg, one hour prior to lumbar discectomy surgery does not reduce postoperative nausea when compared with placebo (110294).

Postoperative pain. It is unclear if melatonin is beneficial for reducing pain postoperatively.

Details: Three meta-analyses, as well as most individual clinical studies, show that taking melatonin in addition to standard therapy modestly alleviates pain and reduces analgesic use after surgery when compared with placebo (62471,62512,62551,62743,88293,88294,103488,103691,103692,105892)(110294,111462). However, any benefit is likely to be small and may not be clinically relevant (103488,109701,111462). Melatonin has been used in doses of 1-10 mg daily for

a duration of 1-21 days, usually starting the night before surgery (62471,62512,62743,103488,103691,105892,110294,111462). This research is limited by poor methodology, as well as the heterogeneity of the included studies. The studies evaluated melatonin across a wide variety of surgeries, including abdominal hysterectomy, cataract surgery, cesarean section, prostatectomy, lumbar laminectomy, lumbar discectomy, laparoscopic cholecystectomy, wisdom teeth extraction, and corrective jaw surgery.

Postoperative recovery. It is unclear if oral melatonin improves the rate of recovery after surgery.

Details: In females undergoing total abdominal hysterectomy, taking extended-release melatonin 5 mg, 90 minutes before surgery, shortens hospital stay to a mean of 2.7 days, compared with 3.4 days for placebo (108945).

Postoperative sleep disturbance. It is unclear if melatonin is beneficial for improving postoperative sleep disturbance.

Details: A meta-analysis of randomized trials in adults undergoing anesthesia for surgery shows that taking melatonin 5-12 mg orally or sublingually or ramelteon 8 mg orally daily for 1-6 days does not improve sleep scores or sleep time when compared with placebo or no intervention (112052). In addition, a small clinical trial shows that taking melatonin (Nature Made) 5 mg each night before bed for 4 weeks, starting 2 weeks after surgery for orthopedic trauma, does not reduce postoperative sleep disturbance when compared with placebo. All patients were also given education related to sleep hygiene (110293).

Postural tachycardia syndrome (POTS). It is unclear if melatonin is beneficial for POTS.

Details: Preliminary clinical research in patients with POTS shows that taking a single dose of melatonin 3 mg reduces sitting and standing heart rate, after 2 and 4 hours, when compared with placebo. However, melatonin does not appear to affect blood pressure or orthostatic symptoms (88292). It is unclear if melatonin is beneficial when taken as more than a single dose.

Pre-eclampsia. It is unclear if oral melatonin reduces the severity of pre-eclampsia.

Details: A small clinical trial in patients with pre-eclampsia shows that taking sustained-release melatonin 10 mg with vitamin B6 10 mg three times daily, starting during recruitment and continuing until delivery, attenuates the need to increase the dose of antihypertensive medication on certain days, but does not affect overall pre-eclampsia severity, when compared with control (99341).

Prostate cancer. Oral melatonin has only been evaluated in combination with medication; its effect when used alone is unclear.

Details: One small clinical study in patients with metastatic prostate cancer that is refractory or resistant to treatment with the luteinizing hormone-releasing hormone (LHRH) analogue triptorelin shows that taking melatonin 20 mg daily in combination with intramuscular triptorelin injected every 28 days can decrease levels of prostate-specific antigen (PSA) and growth factors for prostate cancer when compared to baseline (7255). The validity of these findings is limited by the small study size and lack of a comparator group.

Pruritus. Small clinical trials suggest that oral melatonin might be beneficial for some types of pruritus.

Details: One small clinical trial in patients with pruritus due to various types of chronic liver disease shows that taking melatonin 10 mg nightly for 2 weeks modestly reduces the severity, frequency, and extent of pruritus when compared with placebo (106297). Another small clinical study in patients undergoing hemodialysis shows that taking melatonin 10 mg daily for 2 weeks reduces the severity of pruritus and reduces the affected body area when compared with placebo (104996).

Radiation dermatitis. It is unclear if topical melatonin is beneficial for radiation-related dermatitis.

Details: In females with breast cancer, a small clinical study shows that applying a specific melatonin emulsion cream (Praevoskin, PraevoMed GmbH) twice daily during radiation treatment and continuing for another 2 weeks results in fewer cases of grade 1 or 2 acute radiation dermatitis when compared with placebo (99336). In contrast, another clinical trial in patients with breast cancer shows that applying a cream providing melatonin 25 mg and dimethylsulfoxide 150 mg twice daily during and for 3 weeks after radiation treatment does not improve quality of life or breast symptoms at the end of treatment when compared with placebo. However, there was a modest reduction in breast symptoms over time (110298). Other preliminary clinical research in adults receiving radiation for breast cancer shows that applying melatonin cream 25 mg/gram twice daily throughout radiation therapy does not improve radiation dermatitis scores or reduce the need for adjunctive treatment when compared with placebo (112056).

Rapid eye movement sleep behavior disorder (RBD). It is unclear if oral melatonin is beneficial for RBD.

Details: One very small clinical study shows that taking melatonin 3 mg before bed for 4 weeks increases the likelihood of muscle atonia during rapid eye movement (REM) sleep in patients with RBD when compared with placebo (62762). The validity of this finding is limited by the small study size.

Restless legs syndrome (RLS). It is unclear if oral melatonin is beneficial for RLS.

Details: One very small clinical study shows that taking melatonin 3 mg before bedtime does not improve symptoms of RLS and may actually worsen motor symptoms in individuals with RLS when compared with baseline (62753). The validity of this finding is limited by the small study size and lack of a comparator group.

Rheumatoid arthritis (RA). It is unclear if oral melatonin is beneficial for RA.

Details: A small clinical study in patients with RA shows that taking melatonin 6 mg daily for 12 weeks does not affect disease activity or erythrocyte sedimentation rate (ESR) when compared with placebo (105890).

Sarcoidosis. It is unclear if oral melatonin is beneficial for this condition.

Details: One very small clinical study shows that taking melatonin 20 mg daily for one year, followed by 10 mg daily for another year, improves lung function and skin lesions in patients with chronic sarcoidosis when compared with baseline (62435). The validity of this finding is limited by the small study size and lack of a comparator group.

Schizophrenia. It is unclear if oral melatonin is beneficial for schizophrenia or for attenuating the adverse effects associated with antipsychotic medications.

Details: Some clinical research shows that taking melatonin orally 3 mg each evening for 8 weeks reduces the weight gain and increased waist circumference associated with olanzapine when compared with placebo. It also seems to improve some symptoms of schizophrenia (88296). Other clinical research shows that taking a specific brand of slow-release melatonin (Cronocaps, Productos Medix) 5 mg each evening for 8 weeks reduces adverse effects from second generation antipsychotics, such as increased diastolic blood pressure and waist circumference, when compared with placebo. However, it does not seem to improve symptoms of schizophrenia (88300).

Seasonal affective disorder (SAD). It is unclear if oral melatonin is beneficial for SAD.

Details: Some preliminary clinical research shows that oral melatonin, 0.25-2 mg taken daily for 3 weeks, may decrease winter depression symptoms in patients with SAD (10670,62308). However, sublingual melatonin 0.5 mg daily for 6 days does not appear to improve this condition (62388). Reasons for these discrepancies may include the duration of treatment, route of administration, or the severity of SAD at baseline.

Smoking cessation. It is unclear if oral melatonin is beneficial in patients trying to quit smoking.

Details: One very small clinical study shows that taking melatonin 0.35 mg as a single oral dose 3.5 hours after initiation of nicotine withdrawal in smokers seems to reduce subjective symptoms of anxiety, restlessness, irritability, depression, and cigarette craving over the next 10 hours when compared with baseline (2424). The validity of these findings is limited by the small study size and lack of a comparator group.

Sepsis. It is unclear if oral melatonin is beneficial for sepsis in neonates or adults.

Details: There is conflicting research about the effect of melatonin on neonatal sepsis. While some preliminary research in Egypt shows that giving a single dose of melatonin 20 mg in addition to antibiotics reduces sepsis severity, another more recent study did not find a difference in outcomes between groups receiving antibiotics only or antibiotics with melatonin (99339,99340).

In adults with early septic shock given standard care, a small clinical trial shows that taking melatonin 50 mg daily for 5 days increases the number of ventilator-free days by 6.9 and the number of vasopressor-free days by 2.6. ICU and hospital lengths of stay were reduced by 5.25 and 6.9 days, respectively. However, after 28 days there was no significant difference in the mortality rate, the number of patients requiring ventilation or renal replacement therapy, or the number of patients recovered from organ dysfunction (106296).

Intravenous melatonin has also been investigated. A small clinical trial in patients with severe sepsis shows that a continuous infusion of melatonin, 60 mg over 24 hours, for 5 days following post-surgical sepsis diagnosis modestly reduces sepsis severity when compared with placebo. Hospital stay was reduced by approximately 5.2 days in patients given melatonin; however, it is unclear if this difference is statistically significant (110300).

Stabbing headache. Although there has been interest in using oral melatonin for stabbing headaches, there is insufficient reliable information about the clinical effects of melatonin for this condition.

Stress. It is unclear if oral melatonin is beneficial for stress reduction.

Details: Preliminary clinical research shows that taking melatonin 3 mg one hour prior to stress modestly improves memory accuracy during a laboratory-induced stressful situation when compared with placebo (62509).

Tardive dyskinesia. It is unclear if oral melatonin is beneficial for this condition.

Details: One small clinical study shows that taking melatonin orally 10 mg daily for 6 weeks decreases symptoms by 24% to 30% in patients with tardive dyskinesia when compared with placebo (7082). However, other small clinical studies show that taking melatonin 2-20 mg daily for 4-12 weeks does not reduce abnormal, involuntary movement in patients with tardive dyskinesia when compared with placebo (62146,62825).

Tension headache. It is unclear if oral melatonin is beneficial for reducing the frequency of tension headaches.

Details: A small clinical study in patients with chronic tension headache shows that taking a specific melatonin supplement (Melaxen) 3 mg nightly for 30 days seems to reduce headache severity and reduce the median number of days with a headache by 6 when compared with baseline (104998). The validity of this finding is limited by the lack of a control group.

Tinnitus. It is unclear if oral melatonin is beneficial for improving tinnitus intensity or severity.

Details: Some clinical research shows that taking melatonin 3 mg nightly for one month reduces tinnitus intensity and improves the quality of sleep in individuals with chronic tinnitus when compared with placebo. The effect seems to be greatest in men, those who have not received prior treatment for tinnitus, and those with a history of noise exposure (62820). Other clinical research shows that taking melatonin 3 mg daily for 3 months is more

effective for reducing tinnitus severity than sertraline 50 mg daily (97447). However, other clinical research shows that taking melatonin 3 mg nightly for 30-40 days does not significantly reduce tinnitus intensity when compared with placebo, although the effects might be significant when melatonin is combined with sulpiride or sulodexide (62469,62614).

Traumatic brain injury (TBI). It is unclear if oral melatonin is beneficial for children who have experienced a concussion.

Details: A small clinical study in children ages 8-18 years who have experienced a concussion shows that taking melatonin 3 mg or 10 mg one hour before bedtime for 28 days does not improve persistent post-concussive symptoms when compared with placebo (103690). One small observational study in children in the same age group who have experienced a concussion within 14 days has found that receiving a prescription for melatonin is not associated with improved symptoms and recovery at 15-35 days after concussion (105001). The validity of these findings is limited by small study size and short duration of follow-up.

Ulcerative colitis. Oral melatonin may be modestly beneficial for reducing symptoms or sustaining remission in patients using the medication mesalazine.

Details: A small clinical study shows that taking melatonin 5 mg daily in combination with mesalazine 1 gram twice daily for 12 months may help to sustain remission in patients with ulcerative colitis when compared with mesalazine alone (62821). Another small clinical trial in patients with mild to moderate ulcerative colitis shows that taking melatonin 3 mg daily for 3 months modestly improves overall symptoms, some measures of quality of life, and levels of fecal calprotectin when compared with placebo. However, there was no effect on other markers of inflammation, such as C-reactive protein and erythrocyte sedimentation rate (106303).

More evidence is needed to rate melatonin for these uses.

Dosing & Administration

- **Adult**

  Oral:

  Melatonin has most often been used in doses of up to 8 mg daily for up to 6 months.
  See Effectiveness section for condition-specific information.

  Clinical studies that have evaluated melatonin have used both slow-release and fast-release formulations (89502,89503,89508,96318).

  Intramuscular:

  Research is limited; typical dosing is unavailable.

  Intravenous:

  Research is limited; typical dosing is unavailable.

  Sublingual/Transbuccal:

Research is limited; typical dosing is unavailable.

Topical:

Melatonin has been used in various topical formulations, including as a gargle, cream, and gel.
See Effectiveness section for condition-specific information.

- **Children**

  Oral:

  Melatonin has most often been used in doses of up to 3 mg daily for up to 3 months.
  See Effectiveness section for condition-specific information.

- **Standardization & Formulation**

  In supplements, melatonin is available in tablet, capsule, gummy, chewable, sublingual, and liquid formulations (108144,108145). Clinical studies that have evaluated melatonin have used both slow-release and fast-release formulations. Some of these formulations have been authenticated with certificates of analyses (89503,89508) or have met the United States Pharmacopeia (USP) standards for identity, purity, dose, and stability (89502).

  In the European Union and some other countries, a prescription prolonged-release melatonin product (2 mg, Circadin, Neurim Pharmaceuticals Ltd) is available for treating insomnia in patients 55 years and older. The tablets should not be crushed. There is also a small diameter prolonged-release tablet for pediatric patients (PedPRM, Neurim Pharmaceuticals Ltd), helping to facilitate swallowing in children (96318).

  An analysis of melatonin products available in Canada, including single-ingredient and combination products containing L-theanine, 5-hydroxytryptophan, and/or herbal ingredients, such as lavender, chamomile, valerian, lemon balm, and others, demonstrated high lot-to-lot variability. Melatonin content ranged from -83% to +478% of the labeled quantity. Serotonin, a possible by-product of melatonin biosynthesis or degradation, was found in about 27% of tested products at levels of up to 74.3 mcg/mL (108144). Analyses of gummy products declaring melatonin on the label available in the United States found that one product claiming a melatonin dose of 5 mg per serving did not contain detectable levels of melatonin. The actual quantity of melatonin in the remaining products ranged from 74% to 347% of the labeled quantity, with only 12% of products containing melatonin amounts within 10% of the declared quantity. Only one sample of each brand was analyzed (110328).

Interactions with Drugs

ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **B**

Theoretically, melatonin may have anticoagulant effects and may increase the risk of bleeding if used with anticoagulant or antiplatelet drugs.

Details

There are isolated case reports of minor bleeding and decreased prothrombin activity in people taking melatonin with warfarin (Coumadin) (63067). The mechanism, if any, of this interaction is unknown (9181). Taking melatonin orally seems to decrease coagulation activity within one hour of dosing in healthy men (62481).

ANTICONVULSANTS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **B**

Theoretically, melatonin may reduce the effects of anticonvulsants. Some clinical research suggests that melatonin may increase the frequency of seizures in certain patients, particularly children with neurological impairment (8248,9744).

ANTIDIABETES DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

Theoretically, taking melatonin with antidiabetes drugs might increase the risk of hypoglycemia.

Details

Some clinical research shows that melatonin reduces levels of fasting blood glucose and improves glycemic control (19034,19035,103490). However, other research suggests that melatonin might impair glucose utilization and increase insulin resistance (9713), while other research has found no effect on glucose levels (19036,104368). Until more is known, use melatonin cautiously in combination with antidiabetes drugs.

ANTIHYPERTENSIVE DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **A**

Theoretically, taking melatonin with antihypertensive drugs might increase the risk of hypotension or hypertension.

Details

Some clinical research suggests that taking melatonin decreases blood pressure in healthy adults (1724,62165,62187,63042). Also, melatonin seems to lower systolic and diastolic blood pressure in individuals with high blood pressure at nighttime or untreated essential hypertension (62359,62416,62441,62826). However, melatonin seems to worsen blood pressure in patients who are taking antihypertensive medications. Immediate-release melatonin 5 mg at night in combination with nifedipine GITS (Procardia XL) increases systolic blood pressure an average of 6.5 mmHg, diastolic blood pressure by an average of 4.9 mmHg, and heart rate by 3.9 bpm (6436). Also, results from animal research suggest that melatonin reduces the effectiveness of certain antihypertensive drugs, including methoxamine and clonidine (62432).

CAFFEINE

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Mild • Occurrence = Probable • Level of Evidence = **B**

Theoretically, taking caffeine with melatonin might increase levels of melatonin.

Details

Some evidence suggests that caffeine consumption can decrease endogenous melatonin levels (8265,22303,37585), while other evidence suggests that caffeine increases endogenous melatonin levels (62328). When administered in combination with melatonin supplements, caffeine seems to increase melatonin effects and levels (62352,96315). The reason for this discrepancy is not completely clear. Part of the discrepancy may result from the fact that caffeine can inhibit melatonin synthesis as well as inhibit melatonin metabolism. By functioning as an adenosine receptor antagonist, caffeine may indirectly inhibit the synthesis of melatonin. Conversely, because melatonin and caffeine are both metabolized by cytochrome P450 1A2 (CYP1A2) enzyme, concomitant use of melatonin and caffeine may reduce the metabolism of melatonin, resulting in higher serum levels (22306,96315).

CNS DEPRESSANTS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **D**

Theoretically, taking melatonin might increase the sedative effects of CNS depressants.

Details

Melatonin has sedative effects. Theoretically, concomitant use of melatonin with alcohol, benzodiazepines, or other sedative drugs might cause additive sedation (96315).

CONTRACEPTIVE DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**

Theoretically, taking contraceptive drugs with melatonin might increase the effects and adverse effects of melatonin.

Details

Contraceptive drugs can increase the levels of endogenous melatonin (8265). Theoretically, these drugs may increase the effects and adverse effects of oral melatonin.

CYTOCHROME P450 1A2 (CYP1A2) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Mild • Occurrence = Probable • Level of Evidence = **D**

Theoretically, melatonin might increase levels of drugs metabolized by CYP1A2. Also, other CYP1A2 substrates might decrease the metabolism of melatonin, increasing melatonin levels.

Details

Melatonin is metabolized in the liver primarily by the CYP2C19 and CYP1A2 enzymes (62118,62405,96315). Theoretically, combined administration of melatonin with drugs metabolized by the CYP1A2 enzyme might reduce the metabolism of these drugs, resulting in increased serum levels. Conversely, some drugs metabolized by CYP1A2 may inhibit the metabolism of melatonin, resulting in increased serum levels of melatonin. Until more is known, use melatonin cautiously in patients taking drugs metabolized by these enzymes.

CYTOCHROME P450 2C19 (CYP2C19) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Mild • Occurrence = Probable • Level of Evidence = **D**

Theoretically, melatonin might increase levels of drugs metabolized by CYP2C19. Also, other CYP2C19 substrates might decrease the metabolism of melatonin, increasing melatonin levels.

Details

Melatonin is metabolized in the liver primarily by the CYP2C19 and CYP1A2 enzymes (62118,62405). Theoretically, combined administration of melatonin with certain drugs metabolized by the CYP2C19 enzyme may reduce the metabolism of these drugs, resulting in increased serum levels. Conversely, some drugs metabolized by CYP2C19 may inhibit the metabolism of melatonin, resulting in increased serum levels of melatonin. Until more is known, use melatonin cautiously in patients taking drugs metabolized by these enzymes.

CYTOCHROME P450 2D6 (CYP2D6) SUBSTRATES

Interaction Rating = **Minor** Be watchful with this combination.

Severity = Mild • Occurrence = Possible • Level of Evidence = **D**

Theoretically, melatonin might increase levels of drugs metabolized by CYP2D6.

Details

Laboratory research suggests that certain lots of melatonin inhibit CYP2D6 (96315). Theoretically, combined administration of melatonin with certain drugs metabolized by the CYP2D6 enzyme may reduce the metabolism of these drugs, resulting in increased serum levels. Until more is known, use melatonin cautiously in patients taking drugs metabolized by these enzymes.

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

Interaction Rating = **Minor** Be watchful with this combination.

Severity = Mild • Occurrence = Possible • Level of Evidence = **D**

Theoretically, melatonin might increase levels of drugs metabolized by CYP3A4.

Details

Laboratory research shows that certain lots of melatonin inhibit CYP3A4 (96315). Theoretically, combined administration of melatonin with certain drugs metabolized by CYP3A4 may reduce the metabolism of these drugs, resulting in increased serum levels. Until more is known, use melatonin cautiously in patients taking drugs metabolized by these enzymes.

FLUMAZENIL (Romazicon)

Interaction Rating = **Minor** Be watchful with this combination.

Severity = Mild • Occurrence = Possible • Level of Evidence = **D**

Theoretically, taking flumazenil with melatonin might reduce the effects of melatonin.

Details

Animal research shows that flumazenil may inhibit the effect of melatonin (9703).

FLUVOXAMINE (Luvox)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**

Theoretically, taking fluvoxamine with melatonin might increase levels of melatonin.

Details

Fluvoxamine can significantly increase melatonin levels. In some cases, fluvoxamine might increase bioavailability of exogenously administered melatonin by up to 20 times (5038,6499,8251). Some researchers think this might be a beneficial interaction and be potentially useful for cases of refractory insomnia (6499). However, this interaction might also cause unwanted excessive drowsiness and possibly other adverse effects. Fluvoxamine is known to increase endogenous melatonin secretion (6498,22313). It seems to increase serum levels of exogenously administered melatonin possibly by decreasing melatonin metabolism by inhibiting cytochrome P450 (CYP450) 1A2 and 2C19 or by inhibiting melatonin elimination. This effect has been found in healthy people taking fluvoxamine 50-75 mg and melatonin 5 mg (5038,6498,6499,8251).

IMMUNOSUPPRESSANTS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **B**

Theoretically, melatonin might interfere with immunosuppressive therapy.

Details

Melatonin can stimulate immune function. Theoretically, melatonin might interfere with immunosuppressive therapy (7040).

METHAMPHETAMINE (Desoxyn)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Theoretically, taking melatonin with methamphetamine may increase the adverse effects of methamphetamine.

Details

Animal research suggests that melatonin exacerbates the adverse effects of methamphetamine, resulting in greater depression of tryptophan hydroxylase (TPH) and tyrosine hydroxylase (TH) activity, as well as a significant reduction in dopamine levels (22307). This has not been shown in humans.

NIFEDIPINE GITS (Procardia XL)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**

Theoretically, taking melatonin with extended release nifedipine reduces the effects of nifedipine.

Details

Melatonin can decrease the effectiveness of extended release nifedipine (GITS). Immediate-release melatonin 5 mg at night in combination with nifedipine GITS 30-60 mg daily increases systolic and blood pressure by an average of 6.5 mmHg and 4.9 mmHg, respectively. Concomitant use with melatonin also increases heart rate by 3.9 bpm (6436). The mechanism of this interaction is not known.

SEIZURE THRESHOLD LOWERING DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **D**

Theoretically, taking melatonin with drugs that lower the seizure threshold might increase the risk of seizure activity.

Details

Some clinical evidence suggests that melatonin may increase the frequency of seizures in certain patients, particularly children with neurological disabilities (8248,9744).

WARFARIN (Coumadin)

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **D**

Theoretically, melatonin may have antiplatelet effects and may increase the risk of bleeding with warfarin.

Details

Three cases of increased prothrombin time have been reported for patients aged 48-72 years who took melatonin orally in combination with warfarin (9181). However, three cases of decreased prothrombin time have also been reported for patients aged 51-84 years who took melatonin orally in combination with warfarin (9181). Until more is known, use melatonin cautiously in patients taking warfarin.

Interactions with Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Theoretically, melatonin may have antiplatelet effects in some people.

Details

Theoretically, melatonin might increase the effect of herbs with antiplatelet/anticoagulant activity and might theoretically increase the risk of bleeding in some people (9181,62481,63067). See other products with anticoagulant activity **here**.

CAFFEINE: Theoretically, taking caffeine with melatonin might increase levels and adverse effects of melatonin.

Details

Some evidence suggests that caffeine consumption can increase or decrease endogenous melatonin levels (8265,22303,37585,62328). When administered in combination with melatonin supplements, caffeine seems to increase melatonin levels (62352). The reason for this discrepancy is not completely clear. By functioning as an adenosine

receptor antagonist, caffeine might indirectly inhibit the synthesis of melatonin. Conversely, because melatonin and caffeine are both metabolized by cytochrome P450 1A2 (CYP1A2), concomitant use of melatonin and caffeine might reduce the metabolism of melatonin, resulting in higher serum levels (22306).

HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: Theoretically, taking melatonin with herbs and supplements with hypoglycemic potential might increase the risk of hypoglycemia.

Details

Some clinical research shows that melatonin reduces levels of fasting blood glucose and improves glycemic control (19034,19035,103490). However, other research suggests that melatonin might impair glucose utilization and increase insulin resistance (9713), while other research has found no effect on glucose levels (19036,104368). See other herbs with hypoglycemic effects **here**.

HERBS AND SUPPLEMENTS WITH HYPOTENSIVE EFFECTS: Theoretically, taking melatonin with herbs and supplements with hypotensive effects might increase the risk of hypotension.

Details

Some clinical evidence suggests that taking melatonin decreases blood pressure in healthy adults (1724,62165,62187,63042). Also, melatonin seems to lower systolic and diastolic blood pressure in individuals with high blood pressure at nighttime or untreated essential hypertension (62359,62416,62441,62826). Theoretically, combining melatonin with other herbs and supplements with hypotensive effects might increase the risk of hypotension in some individuals.

HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES: Theoretically, melatonin might have sedative effects.

Details

Theoretically, concomitant use with herbs that have sedative properties might enhance therapeutic and adverse effects (1772). See other products with sedative-hypnotic activity **here**.

SEIZURE THRESHOLD LOWERING HERBS AND SUPPLEMENTS: Theoretically, melatonin might increase the risk of seizures.

Details

Some clinical evidence suggests that melatonin may increase the frequency of seizures in certain patients, particularly children with neurological disabilities (8248,9744). Theoretically, patients taking supplements that also lower the seizure threshold might be at greater risk. See other products with seizure threshold-lowering activity **here**.

VITEX AGNUS-CASTUS: Theoretically, taking vitex agnus-castus with melatonin might increase the effects and side effects of melatonin.

Details

Clinical research in healthy males suggests that taking vitex agnus-castus 120-480 mg daily for 2 weeks significantly increases melatonin levels (62281).

Interactions with Conditions

BLEEDING DISORDERS

Theoretically, melatonin might increase bleeding; until more is known avoid in patients with bleeding disorders. Melatonin has demonstrated anticoagulant activity in some people (9181,62481,63067).

DEPRESSION

Theoretically, melatonin might worsen symptoms in people with depression; until more is known, avoid use in patients with depression. Melatonin has been shown to worsen dysphoria in some people with depression (1764,62384).

HYPERTENSION

Theoretically, melatonin might worsen blood pressure; until more is known, avoid use in people with hypertension. Melatonin has been shown to increase blood pressure in patients who are taking antihypertensive medications. Immediate-release melatonin 5 mg at night in combination with extended-release nifedipine (Procardia XL) increases systolic blood pressure by 6.5 mmHg, diastolic blood pressure by 4.9 mmHg, and heart rate by 3.9 bpm (6436). The mechanism of this interaction is not known.

SEIZURE DISORDERS

Theoretically, melatonin might increase the risk of seizures; until more is known use with caution. Exogenous melatonin may increase the incidence of seizures (9695,9697,9744,62384). Children with multiple neurological disorders, including seizure activity, might have an increase in seizure activity after treatment with oral melatonin for sleep disorders (8248,62754,89431). However, multiple case reports and some clinical research suggests that melatonin actually reduces the incidence of seizure (1699,9746,62123,62256,63070,63071).

TRANSPLANT RECIPIENTS

Theoretically, melatonin might have immunostimulant effects; until more is known, avoid in transplant recipients. Melatonin can stimulate immune function and might interfere with immunosuppressive therapy used by transplant recipients (7040).

Interactions with Lab Tests

None known.

Overdose

Presentation

In the US, cases of pediatric overdose have been reported to poison control centers. From 2012 to 2021, over 260,000 pediatric melatonin ingestions were reported to the American Association of Poison Control Centers' National Poison Data System (NPDS). In 2021, melatonin accounted for 4.9% of all ingestions, compared with only

0.6% in 2012. Most cases were related to unintentional ingestions in children 5 years and under and were asymptomatic. In symptomatic cases, the most common symptoms were related to the central nervous system, followed by the gastrointestinal and cardiovascular systems. Over 4,000 children required hospitalization and almost 300 required intensive care. Also, five children required mechanical ventilation and two children under age five died following unintentional exposure (108145). The dose of melatonin consumed in these cases is unknown. Also, in one case report, a 3-month-old infant who received 8-10 dissolvable melatonin 5 mg tablets daily for an unknown duration was found unresponsive. The child's twin also received similar doses of melatonin without incident. The deceased infant had a melatonin level of 1400 ng/mL, whereas average nocturnal melatonin levels in infants and toddlers are around 0.325 ng/mL. The researchers could not definitively state that melatonin caused this infant's death, citing a lack of evidence on the physiologic effects and reference lab values for melatonin in infants (102514).

Possible melatonin toxicity has also been reported in adults, although in most cases melatonin was taken in addition to other psychotropic medications during a suicide attempt (62822,112439). In one case, a psychotic episode was reported in a 73-year-old female who took a large amount (possibly an overdose) of melatonin (63030).

Treatment

There is insufficient reliable information available about the treatment of overdose with melatonin.

Commercial Products Containing: Melatonin

View All

View Health Canada Licensed Products

View Certified Products

USP Verified Products

NSF Contents Certified Products

NSF Certified for Sport Products

Pharmacokinetics

Absorption: In human research, melatonin supplementation increases plasma levels of melatonin, occasionally into the daylight hours (7081,62424,62439,62807,62787,62908,62917,63013). The bioavailability of synthetic melatonin varies widely, with significant interpatient variability (97436). The calculated oral bioavailability of melatonin from supplements has ranged between 3% to 76% (1126,62908,62917,63013). Within about 1 hour, doses between 1-5 mg lead to serum concentrations 10-100 times those of the usual night-time peak (105005,109698). Lower oral doses such as 0.1-0.3 mg, taken at daytime, lead to peak serum concentrations that are in the normal night-time range (105005). When administered in gelatin capsules, melatonin reaches peak levels after 40 to 150 minutes. The peak levels are 350-10,000 times higher than nighttime concentrations (62916,62917,97436). In human research, the average peak serum concentration is 2630 pg/mL following a 2.5 mg dose, 3550.5 pg/mL following a 10 mg dose, and 64,730 pg/mL following a 75 mg dose (62524,97436). The mean elimination half-life is 40.8 minutes in healthy volunteers

(97436) and 1.8 to 2.1 hours in older adults (92848). Most studies show that levels return to baseline in about 4-8 hours (105005,109698). In healthy patients, a 2 mg dose of a prolonged-release melatonin formulation led to near physiological plasma levels which were sustained for 5-7 hours (96321). Taking a specific prolonged-release tablet (Oniria) results in levels of melatonin that are above normal endogenous levels for at least 8.5 hours (109698). In older adults with insomnia complaints, the time to maximum level, which was 1.3 to 1.5 hours, did not change when doses of 0.4 mg and 2 mg were compared (62848). The maximum concentrations were 405 ± 93 pg/mL and 3999 ± 700 pg/mL (0.4 mg and 2 mg doses, respectively). Use of melatonin 2 mg resulted in a maintenance of melatonin levels >50 pg/mL for an average of 10 hours. The physiologic half-life of melatonin is approximately 30-60 minutes (1072,1742,62905,62917,63013,96318). Nutritional supplements do not appear to mimic the physiologic release of melatonin, as dissolution testing has ranged from 4 to 12 hours (63066,96317), with controlled-release formulations available (62122). The time delay between administration and maximal effect varies linearly from 220 minutes at noon, to 60 minutes at 9 p.m. (63093).

Melatonin may also be delivered transdermally (1058,62946,97448,103489), intravesically, rectally, vaginally (103489), or transmucosally (1058) to mimic physiological activity. Time to maximal concentrations range from 24 minutes with rectal administration to 21 hours with transdermal administration (103489). When a cream containing 12.5% melatonin was applied to 80% of the body surface area of healthy adults, an average peak serum level of 4,977.2 ± 10,369.6 pg/mL was reached at 12 hours (97448).

Distribution: Melatonin levels in saliva are one-quarter to one-third of those in serum and may be used to estimate levels in plasma (62737,62845,62852,62890,108953) and gingival crevicular fluid (62737). Melatonin has also been found in platelets (62790). Melatonin is very lipid-soluble and readily passes through the blood-brain barrier (62243,62477,96322,108949). The volume of distribution for intravenously administered melatonin is 1.2 L/kg (97436).

Metabolism: Melatonin is metabolized in the liver via the hepatic microsome cytochrome P450 system, primarily (but not exclusively) by the CYP2C19 and CYP1A family (particularly CYP1A2) and possibly CYP2C9 and CYP2C19 (6498,48439,62118,62174,62405,96315). First-pass hepatic metabolism, which is extensive (up to 60% of the oral dose) (but can be avoided with the sublingual formulation), includes 6-hydroxylation, followed by conjugation and excretion as the sulfate or glucuronide, and is extensive (62908,62917,63013,96315). Melatonin is deacetylated in the pineal gland and retina to 5-methoxytryptamine (96315). The 6-sulphatoxymelatonin metabolite of melatonin is inactive (62896,62920) and can be determined in serum (62896,62920) and saliva (1743,62845,62890). In patients with liver cirrhosis, melatonin levels are elevated compared to controls due to reduced metabolism (62405,63026).

In case studies in patients with insomnia, a loss of response to melatonin treatment was found to be associated with a slow melatonin metabolism (62765). The authors suggested that in some patients, there may be decreased activity of CYP1A2, resulting in decreased melatonin metabolism and therefore persistent melatonin in plasma at levels of >50 pg/mL up to four hours after supplementation.

Excretion: Urine melatonin levels were found to correlate well with plasma levels (8239). Up to 85% of 6-hydroxymelatonin sulfate was excreted in urine (1751) with a physiologic excretion of 11.1 to 40.2 mcg (19.0 ± 7.4 mcg) in children (62392). In human research, consumption of diets enriched with Jerte Valley cherries (a food source of melatonin) increased urinary levels of 6-sulfatoxymelatonin (62761). In older adults, oral doses of 0.4 mg and 2 mg resulted in an apparent total clearance of 379-478 L/hr (62848). When delivered orally, intravenously, transdermally, intravesically, rectally, or vaginally, the elimination half-life ranged from 45-47 minutes with oral or intravenous administration up to 14.6 hours with transdermal administration (103489,105005).

Mechanism of Action

General: Melatonin is a hormone synthesized endogenously in the pineal gland (1123,1773,62288). It is produced from tryptophan, which is converted to 5-hydroxytryptophan, then to serotonin, then to N-acetylserotonin, and finally to melatonin (1773). The synthesis of melatonin in the pineal gland depends on the norepinephrine-induced stimulation

of post-synaptic pineal beta-1 adrenoreceptors and alpha-1 adrenoreceptors (1773,1780,62173,62868,62877,62885,62924,62926), while alpha-2 adrenoreceptors appear to function as downregulators of melatonin synthesis (62869,62878). The norepinephrine-induced increase in activity and number of alpha-1 and beta-1 adrenoreceptors increases the activity of the enzyme serotonin N-acetyltransferase, which catalyzes the rate-limiting step of melatonin production from serotonin (1773). Following synthesis, melatonin is collected by the venous capillary system, then secreted into the cerebrospinal fluid and the venous systemic circulation (1123,8239). In the brain, melatonin appears to increase the binding of gamma-aminobenzoic acid (GABA) to its receptors by affecting membrane characteristics, not by increasing the number of receptors. Melatonin may decrease neurotransmission by a direct effect on nerve cells (9695).

Melatonin's primary role seems to be regulation of the body's circadian rhythm, endocrine secretions, and sleep patterns (1773,7043). Circadian rhythm of melatonin begins at the end of the neonatal period (62278,62339). Endogenous melatonin is also involved in several other functions including growth hormone secretion and sexual maturation (1776,1777,1778,6497,8246), pain control, balance, and sexual activity (1776,1777,1778,6497). However, it does not appear to directly affect heart function or blood pressure (9714).

Excretion of melatonin is similar in males and females (9747). Melatonin release peaks between one to three years of age. Nocturnal serum melatonin levels naturally decline with increasing pubertal stages (1781,8246,8263). Melatonin suppression by light is not affected by age (1775,62157). However, there is good evidence that melatonin levels can be abnormally low in certain conditions or disease states. Since light inhibits melatonin secretion and darkness stimulates its secretion (1773,62205,62887,62928,63015), people who suffer from an insufficient amount of environmental light often have decreased endogenous melatonin secretion (8247). Infants with low melatonin production are more likely to experience a life-threatening event (ALTE) (8262). Insomniacs of all ages can also have decreased melatonin levels. Patients with sleep disorders related to other conditions, such as fibromyalgia and depression, can also have low levels (6498). Recent information also shows that music therapy can improve endogenous serum melatonin levels in patients with Alzheimer's disease, possibly a contributing factor to patients' relaxed and calm mood (8241). Also, some research suggests that meditation techniques might increase endogenous melatonin concentrations (9748). In other conditions, melatonin's response to light can be altered. For example, in patients with bipolar I disorder, melatonin response to light appears to be abnormal, but is not affected in less severe bipolar II disorder or unipolar depression (1123).

Analgesic effects: Some clinical evidence shows that melatonin may reduce pain associated with conditions such as endometriosis (89503), temporomandibular disorder (89508), fibromyalgia (9701,62797), gastroesophageal reflux disease (62723), irritable bowel syndrome (13112,15216,62410,89510), migraine headaches (6712,12149), and post-operative recovery (62471,62512,62743). Antinociceptive activity of melatonin may be related to the activation of MT1 and MT2 receptors, which reduces cyclic AMP formation and lessens pain; the opening of potassium channels; the inhibition of 5-lipoxygenase and cyclooxygenase-2 expression; and the indirect activation of opioid receptors (62543). However, there does not appear to be a clear relationship between pain perception and urinary concentrations of melatonin metabolites (9700).

Antiaging effects: Melatonin has been identified as countering some of the deleterious effects of aging (62572,62593,62611,62615,62616,62631,62660,62724). Evidence from animal research suggests that melatonin may reduce age-related neurodegeneration by reducing oxidative stress-related impairments and apoptosis that occur in the brain during the aging process (62523). Other animal research has indicated that melatonin may improve longevity (cellular and otherwise) by preventing age-related mitochondrial impairment (62611), maintaining youthful rhythmic activity (62593), improving monoaminergic neurotransmission (62722), and reversing immunosenescence (62567,62565). An experimental model of age-induced neuronal apoptosis indicated that melatonin may exert a protective effect via prosurvival Akt and prevention of DNA damage (62538).

Antiarthritic effects: In vitro, melatonin has beneficial effects on articular chondrocytes, enhancing the synthesis of the cartilage matrix (62519). Melatonin also inhibits the proliferation of fibroblast-like synoviocytes, involved in other types of arthritis (62596).

Antibacterial effects: Preliminary evidence shows that melatonin alone or in combination with isoniazid (INH) is active against some Mycobacterium species (330).

Anticancer effects: According to the "melatonin hypothesis" of cancer, the exposure to light at night and anthropogenic electric and magnetic fields may be related to the increased incidence of cancer and childhood leukemia via melatonin disruption (7042,62447). Patients with endometrial cancer have been found to have melatonin plasma levels that are six times lower than tumor-free controls (62190,63040). Postmenopausal adults with breast cancer have also been found to have lower levels of melatonin when compared with cancer-free controls (101257). Furthermore, some earlier observational research has found that females with estrogen receptor (ER)- or progesterone receptor (PR)-positive breast cancer have lower plasma melatonin levels than those with ER- or PR-negative breast cancer (62906). There is some clinical evidence that taking combined high-dose melatonin with conventional chemotherapy or with interleukin-2 (IL-2) might improve tumor regression rate in patients with breast cancer, lung cancer, kidney cancer, liver cancer, pancreatic cancer, stomach cancer, or colon cancer (1692,5854,5855,5857,7040,7043,8268,62407,62844).

The anticancer effects of melatonin are not entirely clear. In animal models, melatonin appears to protect against the formation of mammary tumors (62321). In vitro, at pharmacological concentrations, melatonin exhibits cytotoxic activity in cancer cells (62211,62248). Melatonin inhibits proliferation and induces apoptosis of various types of cancer cells (1064,5856,7040,9751,62154,62158,62197,62330,62893,62934). At both physiological and pharmacological concentrations, melatonin acts as a differentiating agent in some cancer cells and lowers their invasive and metastatic capabilities through alterations in adhesion molecules and maintenance of gap junctional intercellular communication (62211). In other cancer cell types, melatonin, either alone or in combination with other agents, induces apoptotic cell death.

Biochemical and molecular mechanisms of melatonin's oncostatic action may include regulation of estrogen receptor expression and transactivation, calcium/calmodulin activity, protein kinase C activity, cytoskeletal architecture and function, intracellular pH, melatonin receptor-mediated signal transduction cascades, and fatty acid transport and metabolism (62211). These and other possible anticancer mechanisms may include or operate by modulation of apoptosis (62496,62533,62592,62605,62629,62650), downregulation of HIF-1 alpha expression (antiangiogenic) (62607), antiestrogenic effects (62590,62658,62747), increase in estrogen receptor activity in breast tumors (62921) and decreased expression of estrogen receptors (9711,62828), antiproliferative effects (62587,62674), suppression of linoleic acid uptake and metabolism (62583), SIRT1 inhibition (62572), cytoskeletal dynamics (inhibition of cancer cell migration) (62487,62556), epigenetic regulation (62505), reduction of oxidative stress (62711,62828), enhanced IL-2-induced lymphocytosis (2568), modulation of melatonin receptor expression (62667), stimulation of expression of the growth-inhibitory factor, TGF-beta (62312,62934), nuclear signaling via nuclear RZR/ROR receptors (62296), aromatase activity (62828), G-protein coupled membrane receptors, or via retinoid orphan receptors with involvement of the calcium signaling pathway (62180), and stimulation of melatonin receptors and associated biomolecular cascades (62715).

Melatonin also appears to affect hormones that influence cancer cell growth. For example, it seems to reduce levels of insulin-like growth factor 1 (IGF-1) and prolactin (PRL), which have a role in breast cancer and prostate cell proliferation (1064,5854,5855,5857,7043,7255). Melatonin might also improve survival in patients with cancer by preventing the immunosuppression caused by chemotherapy (7040) or preventing thrombocytopenia associated with cancer chemotherapy by preventing chemotherapy-induced apoptosis of bone marrow cells, and acting synergistically with cytokines to stimulate platelet generation (2564).

However, some conflicting research has not shown that melatonin has oncostatic effects against MCF-7 cells or ZR-75-1 and T-47D cell lines (62340).

Anticonvulsant effects: The relationship between melatonin and seizure risk is controversial. Both anticonvulsant (62318,62525,63071,63081) and proconvulsant (9695) properties have been associated with melatonin in preclinical studies. The production of melatonin is increased in patients with uncontrolled epilepsy. This observation may be explained in two contradictory ways. The brain may be attempting to reduce epileptic nerve transmissions by increasing the concentration of melatonin (9696). In contrast, it may be that melatonin has proconvulsant activity.

Concentrations of melatonin are increased at night and there is also an increased incidence of seizures during the night (9697). It is thought that melatonin might increase seizure activity by affecting the activity of dopamine in the brain (9744). However, many people with seizures have low endogenous melatonin levels, which increase after a seizure occurs. This suggests that melatonin levels increase to compensate for the increased nerve activity that occurs during a seizure (8249). In addition, some anticonvulsant medications increase concentrations of endogenous melatonin (9698), and exogenous melatonin may be used to treat some types of epilepsy (9699). Until more is known about the potential for melatonin to increase seizure activity, it should be avoided in people with seizure disorders (9744).

In animals, intraventricular injection of antimelatonin antibody has elicited transitory epileptiform abnormalities in the electroencephalogram (62915). Proposed mechanisms of action include altered brain GABAergic neurotransmission, interactions with benzodiazepine brain receptors, tryptophan metabolite activity, free radical scavenger activity, or modulation of brain amino acids and nitric oxide (NO) production (9695,62318,62415).

Antidiabetic effects: Melatonin supplementation may impact blood sugar levels both positively and negatively. Although some research has found that melatonin supplementation does not affect glucose levels (19036,63079), melatonin has been reported to elevate blood sugar levels in patients with type 1 diabetes (63036). Also, in postmenopausal patients, low doses of melatonin have reduced glucose tolerance and insulin sensitivity (9713). Furthermore, a large melatonin bolus might also reduce insulin sensitivity. A small clinical study in healthy adult males shows that taking four doses of melatonin 10 mg hourly seems to temporarily reduce insulin sensitivity, but does not affect other glycemic parameters, when compared with placebo (103690).

However, some conflicting evidence has shown beneficial effects. In patients with type 2 diabetes mellitus who had a suboptimal response to the oral hypoglycemic agent metformin, melatonin and zinc acetate administration improved impaired fasting and postprandial glycemic control and decreased the level of glycated hemoglobin (19034,19035). Beneficial effects on glucose levels and insulin sensitivity have also been reported in animal models (62709). Although the mechanism of action is not entirely clear, melatonin may stimulate glycogen synthesis via the PKCzeta-Akt-GSK3beta pathway (62670) as well as inhibit insulin secretion via stimulation of melatonin receptors in pancreatic islet cells (19038). In animal research, melatonin has been suggested as influencing gene expression in insulinoma beta-cells (62618).

Interestingly, endogenous melatonin levels have also shown some correlation with blood glucose levels. However, although endogenous melatonin levels are negatively correlated with plasma levels of insulin, glucose, and leptin in patients with metabolic syndrome (62851), in patients with type 2 diabetes, nocturnal plasma melatonin levels were higher in obese subjects vs. nonobese subjects and lean nondiabetic controls (62856).

Anti-inflammatory effects: In human research, melatonin had anti-inflammatory effects in infants with respiratory distress (62366), and in adults with COVID-19 (106300) or sepsis (110300). In animal research, melatonin has been reported to reduce cardiac inflammatory injury induced by acute exercise (62624). Also in both human and laboratory research, melatonin has been reported to decrease the upregulation of or suppress levels of proinflammatory cytokines (62171,62520,62557,62606,62669,62693,62741,62787). Potential mechanisms of action may include the inhibition of nitric oxide and malondialdehyde (MDA) production or an increase of glutathione levels (62220,62252); the inhibition of phospholipase A2 (62575), mitogen-activated protein kinases (62522), or NF-kappaB (62610,62624,62626,62741); or the regulation of mast cells (62701).

However, some conflicting evidence from clinical research shows that melatonin may not have anti-inflammatory effects. In patients with rheumatoid arthritis, melatonin induced a proinflammatory response, increasing levels of certain inflammatory cytokines, as well as plasma kynurenine concentrations (62460). Also, in patients with ulcerative colitis, melatonin does not reduce levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (106303).

Anti-obesity effects: In patients with type 2 diabetes, nocturnal endogenous plasma melatonin levels have been shown to be higher in obese subjects vs. nonobese subjects and lean nondiabetic controls (62856). However, some evidence from animal and human research suggests that melatonin may play a role in body weight control

(62635,106288). Some evidence from animal models suggests that melatonin inhibits adipocyte differentiation (62635) or reduces gut motility, causing a decrease in appetite (62599). Other animal research has indicated that exogenous melatonin lacks an effect on leptin secretion (62707).

Antioxidant effects: Many of melatonin's proposed therapeutic or preventive uses are based on its antioxidant activity (10671,62120,62191,62216,62227,62239,62240,62245,62251,62258)(62265,62273,62274,62277,62279,62282,62284,62285,62286,62292)(62293,62295,62297,62299,62300,62305,62306,62311,62319,62322)(62326,62460,62471,63087,63091,63092). Preliminary data suggest that melatonin may decrease oxidative renal damage caused by cisplatin (9749). Antioxidant, or free radical-scavenging properties of melatonin have been shown in laboratory and human research against both reactive oxygen and reactive nitrogen species (62202,62212,62216,62238,62240,62251,62279,62286,62292,62295)(62349,62477,62621,62672,62673,62718,62750,62763,62774,62795)(62809,62813,62839,62858,63091,63092,109700,110300). Melatonin may reduce oxidative damage under a variety of conditions in which excessive free radical generation is believed to be involved (30066,62191,62516,62531,62546,62557,62559,62563,62564,62582)(62626,62632,62634,62639,62644,62648,62653,62678,62683,62688)(62692,62726,62733,62735,62736,62738,62744,63087), including animal models of ischemia and reperfusion injury (10671,62120,62227,62239,62245,62258,62265,62273,62274,62277)(62282,62284,62285,62293,62297,62299,62300,62305,62306,62311)(62319,62322,62326,62485,62492,62527,62534,62536,62550,62555)(62562,62566,62568,62603,62625,62641,62666,62698,62739,62740), as well as in nerve tissues, including brain, spinal cord, optic nerve, and spinal cord white matter (62263), and for protection against UV-induced erythema or other damage (1769,62254,63086), protection against stroke-induced neurologic damage (10671,32513,62203,62219,62236,62253,62273,62322), reduced oxidation during blood storage (62842), or protection against other toxins, including heavy metals and radiation (62159,62176,62185,62198,62209,62210,62228,62247,62283,62293)(62300,62306,62323,62326,62931,62976,63051,63056). Melatonin has been reported as being a more efficient antioxidant than glutathione (62294), vitamin C (62235,62255), or vitamin E (7082,62279,62314,62944,62953,62974,63088) and synergy has been observed with other antioxidants (62264,62292). In human research, other potential antioxidant effects of melatonin include an increase in the activity of antioxidant enzymes, glutathione peroxidase, and glutathione reductase (62378,62382). As a result, melatonin has been proposed as a supplement to prevent or treat many conditions that are associated with oxidative damage.

However, a clinical study in preterm neonates shows that oral administration of a single dose of melatonin 0.5 mg/kg at birth does not improve biomarkers of oxidative stress injury at 24 and 48 hours when compared with placebo (107808). Also, animal and other laboratory research has demonstrated a lack of antioxidant effects (62249,62266,62768,62781,62805). Negative effects have even been shown in some research. In animals, melatonin injection increased photoreceptor susceptibility to light-induced damage (62398).

Antiparasitic effects: In animal research, melatonin therapy controlled Trypanosoma cruzi proliferation by stimulating the host's immune response (62649,62652).

Antiviral effects: In animals infected with Venezuelan equine encephalomyelitis virus, administering melatonin 3 days before and 5 days after the infection reduces mortality rates compared to mice administered melatonin along with luzindole, a melatonin receptor antagonist (62497). This suggests that the protective effect of melatonin is mediated by interactions with melatonin receptors.

Blood pressure effects: There is conflicting evidence regarding the effects of melatonin on blood pressure. In animals and humans, research has shown both increases and decreases in blood pressure (1724,8272,9714,62137,62141,62165,62168,62187,62196,62411)(62432,62513,62551,62766,62795,62826,62849,63010)(63042,63082,106299). Some research shows that melatonin has mixed effects depending on the time of day, with decreases at night (62359,62416,62441,62681). However, other research shows that melatonin does not alter blood pressure in animals or humans (62630,62796). Potential mechanisms for antihypertensive effects have been suggested. Melatonin possibly acts via direct effects on the hypothalamus, through antioxidant activity, by inhibiting the sympathetic nervous system and decreasing norepinephrine levels while activating the parasympathetic nervous system, by a direct calcium channel blocking effect, by relaxing smooth muscle in the aorta wall, and by increasing cardiac vagal tone (8272,62226). Other evidence suggests that melatonin lowers blood pressure via GABA(A) receptors (62513), reduces

oxidative load, restores the nitric oxide pathway, and enhances cyclic guanosine monophosphate production in the endothelium (8272,62226,62713,108947). Melatonin also appears to attenuate reflex sympathetic increases in response to orthostatic stress (62324).

Bone effects: In laboratory research, melatonin impaired osteoclast activity and bone resorption through free radical-scavenging and antioxidant methods and promoted osteoblast differentiation (3265,62242,62271). However, in human research, melatonin lacked effects on bone density, N-terminal telopeptide (NTX), or osteocalcin (OC), although the NTX:OC ratio in the melatonin group was reduced (62840).

Cardiovascular effects: Preliminary clinical research shows that serum melatonin levels at nighttime are more than five times lower in patients with coronary heart disease than healthy controls (62941). In addition, following primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction, low levels of platelet melatonin were found to be associated with angiographic no-reflow (62790).

Potential cardioprotective effects of melatonin have been shown in both human and animal research. In humans, the inclusion of melatonin in the combined treatment of cardiovascular disease resulted in anti-ischemic and antianginal effects (62766). Also, melatonin resulted in decreased renal blood flow velocity and conductance, as well as increased forearm blood flow and vascular conductance (62796). Melatonin also increased peripheral blood flow, as measured by distal to proximal skin temperature gradient and finger pulse volume (62355). In animals, fatty streaks were inhibited by melatonin (62237). In models of experimental ischemia-reperfusion, melatonin reduced damage to tissues and limited cardiac pathophysiology (62446).

The potential mechanisms of action have been investigated. Melatonin may act directly on the cardiovascular system rather than modulating cardiac autonomic activity (62344). Relaxation of precontracted rat aorta and reduction of contractile response to alpha-adrenergic but not beta-adrenergic agonists have been observed (62432). However, in contrast to these potential benefits, in animals, melatonin increased the size of atherosclerotic lesions when provided in addition to an atherogenic diet (62230).

Chemoprotective effects: In animal research, melatonin reduced the toxic effects of doxorubicin; malondialdehyde levels were reduced compared to animals given doxorubicin alone (88298).

Coagulation effects: There are isolated case reports of minor bleeding and decreased prothrombin activity in people taking melatonin with warfarin (Coumadin) (63067). Also, in human research, melatonin lowered plasma levels of procoagulant factors (62481). However, in animals, melatonin enhanced platelet responsiveness (62537). Also, it is thought that melatonin plays a role in mediating the influence of the psychoendocrine system and of lighting conditions on hematopoiesis. This is because melatonin regulates hematopoietic cell growth by influencing apoptosis-related mechanisms (1695). Increased platelet counts after melatonin use have been observed in patients with decreased platelets due to cancer therapies (1694,1696,2565,7255,62867,63016,63068). Stimulation of platelet production (thrombopoiesis) has been suggested but not clearly demonstrated. Cases of idiopathic thrombocytopenic purpura (ITP) treated with melatonin have been reported (62260,62289).

Cognitive effects: Although vigilance, reaction time, and tasks in humans undergo circadian variations, they do not seem to correlate with endogenous melatonin levels (1078,62981,63057). Exogenous melatonin may cause decrements in performance, including a slowing of choice-reaction time (62175,62919) or learning (62891). Some studies have failed to confirm a decrement in performance (62332,62356,63080), including a study of high-dose melatonin (50 mg) in elderly persons (mean age: 84.5 years) (63085). Animal research suggests a possible role of the GABAergic system (62215).

Chronic benzodiazepine use leads to decreased levels of melatonin. Supplementation with melatonin is therefore thought to improve the melatonin imbalance and improve sleep quality, especially withdrawal insomnia when benzodiazepines are discontinued (96323). Due to its antioxidant, inflammatory effects, and its modulatory effects on stress and cortisol secretion, there is interest in using melatonin for reversal of cognitive dysfunction that occurs during benzodiazepine withdrawal. However, current clinical research does not support melatonin for this use (96322).

Dental effects: In human research, salivary and gingival crevicular fluid melatonin levels were lower in individuals with periodontal disease (62737). The effect of supplementary melatonin on symptoms of periodontal disease is not clear.

Dermatologic effects: Dermatologic use of melatonin has been proposed because of its immunomodulatory and antioxidant abilities. Study findings indicate that melatonin may accumulate in the stratum corneum (1768). In human research, free radical scavenging was suggested as a possible mechanism of action in the protection against UV-induced erythema (1769).

Exercise performance effects: Melatonin may have beneficial effects during exercise. In human research, in combination with exercise melatonin increased the area under the curve of growth hormone (62424) and protected against the overexpression, or inhibited the expression, of inflammatory mediators (62813). Melatonin also decreased exercise-induced increases in triglyceride levels and improved antioxidant status (62839).

Endocrine effects: In clinical and laboratory studies, melatonin has been reported as producing varying hormonal effects. Such reports include changes in levels of cortisol in some, but not all, studies (62346,62350,62720,62755,62975,62987,63044), progesterone (769,62369,62685,62812,62987), estradiol (769), thyroid hormone (T4 and T3) (2425,62225,62507), testosterone (62244,62507), growth hormone (1076,1741,1777,1779,62884,62913,62922), prolactin (62182,62411,62883,62922,62978,63044,63072), oxytocin and vasopressin (1779,62680,62719,63017,63050), adrenocorticotrophic hormone (62350), thyroid-stimulating hormone (TSH) (62383), and gonadotropin-inhibitory hormone (62697).

Melatonin also appears to affect levels of luteinizing hormone (LH) (1741,62133,62136,62515,62863,62936,62938,62989). However, the LH response to melatonin was found to be distorted in patients with menstrual abnormalities (62608,62871), was absent in postmenopausal adults (62918,62943), and was not observed in males (62773,62876,62925), in whom only a decrease in basal luteinizing hormone level was noted (1741,62133,62136).

In humans, although melatonin did not change basal oxytocin secretion, the oxytocin response to insulin-induced hypoglycemia was reduced (63052). Enhanced growth hormone levels may be mediated via the serotonin pathway (62442,62911,62912) or through naloxone-sensitive opioid-mediation (62888,63053); however, this effect has not been confirmed in other studies (62898,62927).

Under stimulus situations and in combination with estradiol treatment, melatonin reduced peak values of norepinephrine and increased epinephrine levels in humans in some, but not all, studies (9704,62152,62509,63010). In human research, during a heavy-resistance exercise session, melatonin increased the area under the curve of growth hormone (62424). It has been proposed that administering melatonin to aging females may lead to a recovery of pituitary and thyroid function (2425,11806). Although it has been suggested that melatonin may modulate hypothalamic-pituitary-thyroid axis function and affect body temperature (62383), in healthy young men, melatonin lacked an effect on suppressing hypothalamic-pituitary-adrenal system activity (62411). Research has suggested that melatonin may mimic the effect of drugs that act through the estrogen receptor interfering with the effects of endogenous estrogens, as well as those that interfere with the synthesis of estrogens by inhibiting the enzymes controlling the interconversion from their androgenic precursors (62395).

Some evidence suggests that melatonin peak time (acrophase) is advanced in postmenopausal adults when compared with premenopausal adults (89432). Some clinical evidence suggests that hormone replacement therapy does not affect serum levels or the duration of endogenous melatonin secretion, but it does appear to delay melatonin acrophase by 2.4 hours in postmenopausal adults after about 6 months of treatment (89507). Theoretically, some of the positive effects of hormone therapy in postmenopausal adults may be related to its ability to delay advanced melatonin peak time.

Gastrointestinal effects: Research has been conducted concerning the effects of melatonin in patients with duodenal ulcers, dyspepsia, gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), and ulcerative colitis. In patients with GERD, a melatonin-containing supplement inhibited gastric acid secretion and synthesis of nitric oxide (16011); nitric oxide affects lower esophageal sphincter relaxation, a major mechanism. Melatonin may also regulate

pancreatic secretion and maintained the integrity of the pancreas (62448), affect bowel functions, reduce gut contractions induced by serotonin, and inhibit proliferation of epithelium, (62970). In animals, high doses of melatonin have been shown to inhibit motility by interacting with serotonin and CCK2 (62417). Protective effects of melatonin in the gastrointestinal tract may be due to its effects on prostaglandins and cytoprotection from its free radical-scavenging activity (62193,62267,62325,62349,62477,62478). In animal models of gastric ulcer, beneficial effects of melatonin may be due to the downregulation of matrix metalloproteinases-9 and -3 (62591). Melatonin showed similar benefit in a model of NSAID-induced gastropathy by preventing activation of the mitochondrially mediated apoptosis (by mitigating oxidative stress) (62542).

Graft effects: In animals, melatonin improved the survival of human-derived ovarian grafts (62832). The mechanism of action is unclear.

Hepatoprotective effects: Various hepatoprotective effects of melatonin have been shown in humans. In patients with nonalcoholic steatohepatitis (NASH), use of melatonin resulted in improvements in liver function (62853). In patients with steatohepatitis, melatonin decreased levels of proinflammatory cytokines, triglycerides, and GGTP (62787). Also, decreased transaminases have been shown following liver resection (62807).

Hypolipidemic effects: In human and animal research, melatonin reduced cholesterol levels (62787,62795,62839,63025,110291). However, there is some evidence of increases in very low-density lipoprotein (VLDL)-cholesterol and triglyceride levels in human research (62176).

Immune effects: Researchers have conducted studies concerning the effects of melatonin as they relate to cachexia, chemotherapy side effects, HIV/AIDS, ischemia-reperfusion injury, and sepsis. Researchers noted increased platelet counts after melatonin use in patients with decreased platelets due to cancer chemotherapy (1694,1696,2565,7255,62464,62867,63016). Although not clearly demonstrated, studies have indicated possible stimulation of platelet production (thrombopoiesis). Melatonin has been reported to promote neutrophil apoptosis in patients receiving hepatectomy involving ischemia and reperfusion of the liver (62293,62300,62306,62326). Preliminary clinical studies suggest that combined therapy with low-dose subcutaneous IL-2 and melatonin improved the immune status in AIDS patients with CD4 cell counts below 200/mm^3, who generally do not respond to IL-2 alone. The mean number of lymphocytes, eosinophils, T lymphocytes, natural killer (NK) cells, and CD25- and DR-positive lymphocytes increased with the treatment. An increase in the subjects' CD4:CD8 mean ratio was noted (63002). In cancer patients who achieved disease control, melatonin induced a decrease in the number of regulatory T lymphocytes; this change was lacking in individuals with progressed disease (62783). A combination hormone therapy including melatonin was found to improve leukocyte function in ovariectomized aged rats (62567).

Activation of melatonin receptors has been associated with the release of cytokines by type 1 T-helper cells (Th1), including gamma-interferon (gamma-IFN) and IL-2, as well as novel opioid cytokines (62167). There is indirect evidence that melatonin may amplify the immunostimulatory effect of IL-2, as measured by an increase in the number of T-lymphocytes, natural killer cells, and eosinophils in cancer patients (7043,62301,62334,62977,62983). In animal research, inhibition of the circadian synthesis of melatonin has been associated with reversible immunosuppression (62881) and elicited T cell autoimmunity in mice (62954,63032).

Administration of melatonin agonists has reportedly reduced neophobia, and treatment with a melatonin antagonist during the dark period has reportedly reversed the anxiolytic-like effect of endogenous melatonin (62288). A study in rats showed that melatonin attenuated kainic acid (KA)-induced neuronal death, lipid peroxidation, and microglial activation, and the number of DNA breaks (62272). Other mechanisms through which melatonin may modulate the immune system, according to laboratory research, include the following: suppression of TNF-alpha, IL-1 beta, and IL-6 (62520); inhibition of Th1 cells (62647); stimulation of humoral activity/antibody production (62532,62628,62695); inhibition of NF-kappaB (62541), IKK, and JNK pathways (62485); prevention of T cell apoptosis (62742); and stimulation of mononuclear cell production (62687).

Neurologic effects: It has also been proposed that melatonin may reduce the amount of neurologic damage patients experience after stroke, due to its antioxidant properties (10671,32513,62203,62219,62236,62253,62273,62322). Melatonin

has also been suggested as a possible therapeutic strategy for Alzheimer's disease, having been shown in laboratory study to attenuate amyloid-beta-induced phosphorylation of tau-protein and prevent GSK-3beta activation and neuroinflammation (62732), and mitigate amyloid-beta-mediated mitochondrial dysfunction (62712) and amyloid-beta load (62659). Also, in vitro evidence suggests that melatonin may inhibit the biochemical processes involved with the development of myeloid plaques found in the brains of patients with Alzheimer's disease; however, the clinical significance is unclear (9710). Possible neuroprotective mechanisms include the prevention of FGF9 downregulation (62581), the prevention of the induction of mitochondrial NO synthase (62571), or the inhibition of 6-hydroxydopamine production (62663). Other animal research has indicated that melatonin preserved hippocampal cytochrome oxidase and sirtuin-1 expression following sleep deprivation (62623). According to a review, melatonin mechanisms related to a reduction in headache pathophysiology include its anti-inflammatory effect, toxic free radical scavenging, reduction of proinflammatory cytokine upregulation, nitric oxide synthase activity and dopamine release inhibition, membrane stabilization, GABA and opioid analgesia potentiation, glutamate neurotoxicity protection, neurovascular regulation, 5-HT modulation, and its similarity in chemical structure to indomethacin (62425).

However, in a rodent model of Parkinson's disease, melatonin was found to potentiate neurodegeneration (62637). Also, although a number of preliminary animal studies have also suggested that melatonin may aid in recovery from or mitigate spinal cord injury (62327,62522,62751), not all findings have been positive (62498).

Opioid tolerance effects: In animals, researchers have concluded that melatonin acutely reversed and prevented tolerance to and dependence on morphine (62126,62276), and reduced the incidence of naloxone-induced withdrawal (62126); however, the exact mechanism is not well understood.

Optic/ocular effects: In human research, melatonin stabilized vision in patients suffering from age-related macular degeneration (62419) and decreased intraocular pressure in the eye (62551,62889,62961). However, information in available reviews suggests that high doses of melatonin may increase intraocular pressure and the risk of glaucoma, age-related maculopathy, and myopia (63036), as well as retinal damage (63003).

Psychiatric effects: In patients with schizophrenia, melatonin lacked effects on P50 suppression, suggesting a lack of effect on sensory gating in these patients (62846). However, increases in the P50 ratio occurred in some individuals with high baseline P50 suppression.

Radioprotective effects: Animal and in vitro research has shown that melatonin possesses a protective effect against damage caused by ionizing radiation (62504,62577,62609,62661,62662,62696,62734). The specific mechanisms may involve downregulation of apoptotic pathways via control of oxidative load (62511). Furthermore, there is interest in whether melatonin might be protective against medical imaging radiation. One in vitro study suggests that X-ray radiation of 100 mGy seems to result in fewer double-stranded DNA breaks in blood samples taken from volunteers after melatonin ingestion when compared with blood samples taken before melatonin ingestion (104999). However, a clinical study in females with hyperthyroidism receiving 10-20 mCi iodine-131 shows that taking melatonin 300 mg prior to radioiodine therapy has no effect on chromosomal damage when compared with placebo (107810).

Reproductive effects: Due to its antioxidant potential and role in determining sexual status in certain mammals, melatonin has been suggested as a means of improving reproductive success in a variety of conditions (62573). In animals, exposure to exogenous melatonin increased sperm motility, ejaculate volume, sperm concentration, total sperm output, total function sperm fraction, and blood testosterone concentration, and decreased means of reaction time, dead sperm, abnormal sperm, and blood triiodothyronine concentration (62507,62689) and regulate follicular development and oocyte competence (62604,62612).

Also, melatonin implants have been shown to improve semen characteristics (62686). Additional veterinary research has indicated that melatonin may increase reproductive success (62486,62502,62589) or activity, depending on the dose (6497,62627) and improve the viability of embryos produced with in vitro fertilization (62488,62490,62549,62668,62731). There is preliminary evidence that very high melatonin doses plus norethisterone can have additive or synergistic effects on inhibiting ovarian function and possibly act as a contraceptive (769). In vitro, melatonin has been shown to decrease kisspeptin gene expression, while increasing that of RFRP-3 in cell lines from rat hypothalamus (62576). In

other research, melatonin lacked an effect on luteal blood flow or function in humans (62528). In a rat model of endometriosis, melatonin was shown to induce regression of endometriotic foci (62682). Other reproductive applications of melatonin include the suppression of estrus (in cats) (62594), induction of estrus (in goats) (62588), and inhibition of gonad function (in fish) (62585).

Sleep effects: Melatonin, administered in the day or night in doses beyond the physiological range, appears to elicit a hypnotic effect. Various studies have been conducted in humans. For example, exogenous melatonin exerted hypnotic effects primarily when circulating levels of endogenous melatonin were low (1758) and even very low doses may cause sleep when ingested before endogenous melatonin onset (1078,1753,1756,62947,62997), although some studies have failed to confirm this finding (62895). Functional magnetic resonance imaging suggests melatonin may play a role in priming sleep-associated brain activation patterns in anticipation of sleep (62420). Also, melatonin has been shown to decrease the amount of anesthesia required during surgery (62233,62430,62443,62444) and potentiate the effects of gamma-aminobutyric acid (GABA) and benzodiazepines, and improve quality of sleep in combination with benzodiazepines (62964). Melatonin may interact directly with the GABA-benzodiazepine-chloride ion channel as suggested in both human and animal research (62183,62269), but not with the benzodiazepine receptor as suggested in human research (63005).

Randomized clinical trials have demonstrated some effect of melatonin on circadian rhythm entraining (62207,62377,62409). Endogenous circadian rhythmicity influences autonomic control of heart rate, and the timing of these endogenous rhythms may be altered by extended sleep/rest episodes and associated changes in the photoperiod, as well as by melatonin treatment (62461), with no evidence of changes in the duration of endogenous melatonin secretion or pituitary or gonadal hormones (62335). In visually impaired individuals, disturbances of sleep and sleep-related neuroendocrine patterns may be caused by the absence of light cues as the lack of light signal in blind persons leads to various unusual free-running melatonin secretory patterns (62367,62923,62929). Also, people who suffer from an insufficient amount of environmental light often have decreased endogenous melatonin secretion (8247). In individuals who are completely blind, a single administration of a pharmacological dose of melatonin improved sleep function by synchronizing the inhibition of pituitary-adrenal activity with central nervous sleep processes (62350). Disturbances in the circadian rhythm of melatonin (and declines in nighttime melatonin) have been associated with aging (1773,1775,1781,62134,62116,62170,62900,63046). In human research, exogenous melatonin is able to shift circadian rhythms, as well as endogenous melatonin secretion and core body temperature (62418,62945,63001,63023). However, light appears to be a stronger regulator of circadian rhythm than melatonin itself (8274,62960,62986,62999,63008,63015,63018,63033). The time of administration of melatonin is of critical importance, since it may cause both phase delay and phase advance. In human research it was determined that for phase delay, melatonin should be administered in the early morning; however, for phase advance, melatonin should be administered 1-2 hours before 9 p.m. (8274).

Clinically, melatonin is used in many disease states thought to have low levels of melatonin such as traumatic brain injury and Alzheimer's disease (62847,96317,96319,96320). Decreased membrane fluidity is thought to play a role in the pathogenies of Alzheimer's disease. Stress and rapid eye movement contribute to neuronal rigidity. Melatonin has been added to other ingredients to help promote sleep and improve cognition in patients with Alzheimer's disease (62847). Additionally, in patients with depression, the circadian rhythm is altered. Patients with depression often have insomnia and early-morning awakening. It has been hypothesized that low melatonin secretion is a marker of depression, and melatonin may improve these symptoms, although the majority of clinical research does not support melatonin for this use (96326).

Low-dose melatonin has been noted to be more effective entraining blind people with a free-running melatonin secretory pattern due to the potential of excess hormone discharging into the wrong zone of the phase-response curve (62232). Free-running patterns are also observed after pineal gland damage (62952) or under special working regimens (62901,62955). The nocturnal onset of melatonin secretion strongly correlates with a steep rise in sleep propensity and precedes it by approximately two hours (63047). The specific events taking place during this interval currently remain obscure. It is possible that melatonin does not actively induce sleep but switches off a wakefulness-generated mechanism that opposes a sleep-inducing mechanism (63047), the alerting process being dependent on the suprachiasmatic nucleus (63039).While measuring endogenous melatonin, some authors have not found a link

between melatonin secretion and the sleep-waking cycle in humans (62899). It has been suggested by some that natural sleep is largely determined by a functioning circadian system without melatonin involvement (62886,62949,63045,63046).

Thermoregulating effects: The central thermoregulatory centers, including the preoptic area of the anterior hypothalamus, are likely to be involved with the regulation of core temperature following melatonin administration (1132). In human research, hypothermic effects of melatonin have been reported with doses from 15mg (1757,62418,63007) and ingestion of melatonin 1.6 mg was reported to result in approximately 0.4 °C decrease of body temperature in humans (62418,62945,63001,63023). The hypothermic effects may be mediated by GABA receptor activity (63063). Melatonin may also influence chloride flux or other intracellular actions via a different mechanism that is not well understood (63005). Melatonin did not appear to exert hypothermic effects by central benzodiazepine receptors (63005). Melatonin appeared to increase heat loss and decrease heat production when taken during the day (63063). A parallel relationship was found between rectal core body temperature and the decline in sleep onset latency following melatonin administration (63063).

Toxicity protective effects: A number of laboratory studies have established melatonin's ability to prevent or mitigate damage from a number of chemical sources, including (but not limited to) methamphetamines (62563,62717), organophosphorus compounds (62493,62494,62664), alcohol (62636,62675), nicotine (62716), beta-cyfluthrin (62700), and benzo(a)pyrene (62694).

Vestibular effects: In human research, melatonin attenuated the muscle sympathetic nerve activity (vestibulosympathetic reflex) response to baroreceptor unloading, while lacking effects on the vestibulocollic reflexes (62779). In human research, melatonin positively benefitted balance (1776).

Weight loss effects: Melatonin may inhibit preadipocyte differentiation into adipocytes. It may also increase the metabolic rate and energy expenditure by converting white adipose tissue to brown (96316).

Classifications

Anticoagulant Agents, Cytochrome P450 2D6 (CYP2D6) Inhibitors, Cytochrome P450 3A4 (CYP3A4) Inhibitors, Immunomodulators, Sedative-Hypnotic Agents, Seizure Threshold-Lowering Agents, Vasodilators

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References

See Monograph References

Monographs are reviewed on a regular schedule. See our Editorial Principles and Process for details. The literature evaluated in this monograph is current through 11/16/2023. This monograph was last modified on 3/7/2024. If you have comments or suggestions, please tell the editors.