REFERENCE SHEET:

Melatonin

Pronunciation

Melatonin (mel-ah-tow-nin)
5 methoxy-N-acetyltryptamine

Summary

Melatonin is a hormone produced by the pineal gland and synthesized from tryptophan and serotonin. It can also be produced by enterochromaffin cells in the GI tract. Melatonin is primarily involved in the regulation of sleep patterns. Endogenous melatonin increases as the retinas signal the pineal gland with diminishing light, providing crucial information in the regulation of sleep-wake cycles and core body temperatures. Approximately 80% of melatonin is synthesized at night, with the greatest rate of synthesis between 2 am and 4 am. Melatonin plays a role in circadian rhythm regulation, reproduction, mood, and immunity. It also has anti-oxidative effects and possesses properties that protect against pain, inflammation, and anxiety. Infants produce very little melatonin; a production rhythm develops after three months of age. Melatonin production peaks between the ages of four and seven before progressively declining with age.

Main medical uses

For general use, meta-analyses indicate that melatonin reduces sleep latency, increases total sleep time, and improves sleep quality in adults and children.

Melatonin is used to treat primary sleep disorders, including insomnia, delayed sleep phase syndrome (DSPS), rapid eye movement sleep behavior disorder (RBD), jet lag, and sleep-wake patterns disrupted from blindness. It can also be used to treat sleep disorders secondary to other conditions, including asthma, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, autism spectrum disorder (ASD), beta-blocker-induced insomnia, bipolar disorder, cystic fibrosis, depression, epilepsy, neurodevelopmental disorders, Parkinson's disease, schizophrenia, traumatic brain injury, and tuberous sclerosis.

Beyond its use for sleep, melatonin may also improve presurgical anxiety and sedation, reduce rates of radiotherapy- and chemotherapy-induced side effects, reduce pain in endometriosis and temporomandibular disorders, treat or prevent seasonal affective disorder (SAD), and treat nocturnal hypertension, chronic fatigue syndrome (CFS), fibromyalgia, gastroesophageal reflux disease (GERD), migraines and cluster headaches, age-related macular degeneration (AMD) and central serous chorioretinopathy (CSC), atopic dermatitis in children, irritable bowel syndrome (IBS), and polycystic ovarian syndrome (PCOS). Melatonin has also been shown to improve seizure frequency, quality of life, and antioxidant profiles in patients with epilepsy and multiple sclerosis.

Formulations

Intake of oral melatonin (1-5 mg) typically results in increased plasma levels of up to 100 times greater than the natural nocturnal peak concentration. However, the speed at which this occurs may vary based on the formulation and/or method of administration.

Time to achieve max plasma/serum concentrations (Cmax):

- Intranasal administration: ~10 minutes (0.4 mg)
- Intravenous administration: ~5 minutes (0.2 mg)
- Oral tablets: ~40 minutes (5 mg)
- Oral tablets (slow-release): ~2 hours and 45 minutes
- Sublingual spray: ~40 minutes (5 mg) with higher Cmax than oral tablets.
- Transdermal patch: ~8.5-13 hours (2.1-8 mg)
- Transdermal nanoparticle gel: ~13-18 hours (3.6 mg)
- Transmucosal patch: 8 hours (0.5 mg)

Dosing and administration

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Atopic dermatitis	3-6 mg per day, one hour before bedtime for 4-6 weeks in children	↓ SCORAD index, and sleep onset latency ↓ IgE levels at higher doses	B	↓ IgE in humans ↓ IL-4 and IFN-γ secretion by activated CD4(+) T cells and IgE in mice
Beta-blocker-induced insomnia	2.5 mg adjunct to atenolol 25-100 mg/day) or metoprolol (50-100 mg/day) 1 hour before bedtime for 3 weeks in adults	↑ total sleep time, sleep efficiency, and Stage 2 sleep; ↓ sleep onset latency which persists upon discontinuation	C	↑ melatonin levels despite pineal gland inhibition by beta-blockers ↓ core temperature
Blindness-associated sleep disturbances	10 mg per day, 1 hour before bedtime until entrainment achieved and taper-reduced to 0.5 mg over 3 months in adults 5 mg (slow-release) per day 1-2 hours before bedtime for 3-6 weeks in adults	↑ sleep duration; ↓ time awake after 1st sleep onset, and day-time napping ↑ sleep duration to a clinically relevant degree, but with no statistical significance	C C	Entrains free-running circadian rhythm from 24.2-24.9 hours to 24 hours, which persists even after tapering to a minimal dose Advances melatonin phase and shifts cortisol phase in tandem Normalizes temporal ACTH and serum cortisol pattern by suppressing pituitary-adrenal activity in early sleep phases and causes a rise in activity in late phases
Central serous chorio-retinopathy	3 mg three times per day for 1 month in adults	↑ best-corrected visual acuity; ↓ central macular thickness	C	Proposed mechanisms: ↓ VEGF that may damage the blood-retinal barrier, glucocorticoids, and retinal ROS
Cluster headaches	10 mg per day in the evening for 2 weeks	↓ cluster headache frequency within 3-5 days; Headaches may resume upon discontinuation	C	Proposed mechanism: May balance melatonin levels that are often reduced in cluster headache px

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Delayed sleep phase syndrome	5 mg per day, 3-4 hours before bedtime for 2-4 weeks in adults	↓ sleep onset latency, wake time and total sleep time, reports of sleepiness and fatigue, and nocturnal melatonin profile onset by ~1.5 hours	C	Advances the nocturnal melatonin profile onset by ~1.5 hours
	5 mg per day in the evening for 4 weeks in adults with depressive symptoms	↓ CES-D and Hamilton Depression Rating Scale-17 depression scores, and sleep discontinuity	C	
	0.3-3 mg (slow-release) per day, 1.5-6.5 hours before dimming of light for 4 weeks in adults	↓ time to melatonin production from circadian phase, with greater efficacy the earlier the administration before dim light	C	
Endometriosis	10 mg per day at bedtime for 8 weeks in adults	↑ sleep quality; ↓ pain and dysmenorrhea by ~40%, risk of use of other analgesics by 80%, and BDNF levels	C	↓ BDNF levels in humans ↓ MDA, COX-2, MMP-9, MMP-3, and VEGF; ↑ SOD and CAT activities, TIMP-1, and caspase-3 mediated apoptosis in endometriotic tissues of rodents ↓ steroidogenesis, intraperitoneal adhesions, and anti-mesometrial stromal cell proliferation in rodents

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Epilepsy	3 mg per day, 30 minutes before bedtime adjunct to AEDs for 3 months in children 6 mg (<30 kg; < age of 9) to 9 mg (>30 kg; >age of 9) (fast- or slow-release) as add-on therapy to AEDs within 1 hour of bedtime for 4-8 weeks in children	↓ seizure frequency especially at night; ↑ sleep efficiency and continuity ↑ GSH-Px and GSSG-Rd activities Improves attention, memory, language subscale scores in measures of QoL	C C	↑ GSH-Px and GSSG-Rd activities in humans ↓ NMDA excitation via increased GABA activity, and neuronal damage; ↑ electroconvulsive threshold in rodents
Fibromyalgia	3-5 mg alone or combined with fluoxetine, or 10 mg alone or combined with amitriptyline per day for 6-8 weeks in adults	↓ pain, and Fibromyalgia Impact Score (FIQ) scores; ↑ inhibitory action of the endogenous pain-modulating system	B	↑ inhibitory action of the endogenous pain-modulating system ↑ pain threshold in humans, possibly via increased opioid and benzodiazepine-GABAergic pathways
Insomnia (primary)	0.05-0.15 mg/kg, or 5 mg per day, 1-2 hours before dim-light onset for 1-4 weeks in children	↓ time to 'lights-off', sleep onset and melatonin onset, sleep offset, and sleep latency; ↑ sleep duration, general health scores, and function status scores Sleep onset, onset latency and dim-light melatonin onset increases with earlier circadian time of administration	B	Proposed mechanisms: Increases in physiological melatonin levels bind to MT1 and MT2 receptors in the suprachiasmatic nucleus to regulate the phase and amplitude of the circadian rhythm. MT1 may suppress neural activity while MT2 may shift phases in the rhythm in rodents

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Insomnia (primary)	0.3-2 mg (slow-release) per day, 1-2 hours before bedtime after the evening meal for 3-weeks to 6 months in the elderly with melatonin deficiency	↑ sleep quality/efficiency, maintenance, morning alertness, QoL, and Clinical Global Impression (CGI) scores; ↓ sleep-latency, sleep initiation time, and wake-time after sleep onset May improve daytime psychomotor performance No withdrawal upon discontinuation, or build up of tolerance	B	Proposed mechanisms: Increases in physiological melatonin levels bind to MT1 and MT2 receptors in the suprachiasmatic nucleus to regulate the phase and amplitude of the circadian rhythm. MT1 may suppress neural activity while MT2 may shift phases in the rhythm in rodents
Irritable bowel syndrome	3-5 mg per day at bedtime for 2-8 weeks in adults	↓ abdominal pain, bloating and constipation; ↑ rectal pain threshold Improves overall IBS, extracolonic IBS, and QoL scores	B	↑ colonic transit time in constipation-dominant IBS but time reduces in healthy individuals Px with gastric pain have reduced melatonin and lower temperature-rhythm amplitudes ↓ nitrergic myenteric innervation
Jet lag	0.5-5mg (fast-release) close to bedtime at the destination of travel for 3 days prior to flight and 3-5 days post-flight in adults	↓ jet-lag symptoms including compromised sleep quality, greater time to sleep onset, fatigue and daytime sleepiness, and days to normalize sleep patterns; ↑ rate of jet-lag prevention Most effective when traveling east and over 5 time zones.	A	Exogenous melatonin may partially counter circadian phase-shifting responses induced by the changing perception of light Correctly timed melatonin administration may boost phase-shifting induced by the changing perception of light
	2 mg (slow-release) at night at the destination of travel for 4 days after arrival in adults	↓ time to fall asleep, number of awakenings and time spent awake after sleep onset; ↑ sleep duration and quality to the same extent as zopiclone May not be as effective as fast-release formulations	C	

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Migraine	3 mg (fast-release) or 4 mg (slow-release) for < 3 months in adults	↑ migraine prophylaxis with similar efficacy to amitriptyline	A	Proposed mechanisms: ↑ anti-inflammation, ROS scavenging, delta-opioid activity, and membrane stability; ↓ dopamine release; modulates serotonin, GABA and glutamate neurotransmission and cerebrovascularity
Multiple sclerosis	25 mg per day, 1 hour before bedtime for 6 months in adults	↓ serum pro-inflammatory cytokines and markers of oxidative stress	C	↓ TNF-α, IL-1β, IL-6, lipoperoxides, nitric oxide catabolites ↓ MDA with concurrent interferons-beta and glatiramer acetate but not mitoxantrone; ↑ SOD activity with interferons-beta ↓ pathogenic Th17 cell differentiation; ↑ protective Tr1 cells
Nocturnal hypertension	2-3 mg (slow-release) per day, 1-2 hours before bedtime for 3-4 weeks in adults 1.5-2 mg per day, 1-2 hours before bedtime for 2-4 weeks in the elderly	↓ SBP and DBP ↓ SBP and DBP	A C	↓ internal carotid artery pulsatility index, sympathetic activity, dopamine, and norepinephrine ↑ nitrites/nitrates
Polycystic ovarian syndrome	10 mg per day, 1 hour before bedtime for 12 weeks in adults	↑ sleep quality, insulin sensitivity, and PPAR-γ and LDL-R expression; ↓ anxiety and depression scores, insulin, HOMA-IR, total cholesterol, and LDL-C	B	↑ PPAR-γ and LDL-R expression, and insulin sensitivity; ↓ insulin, insulin resistance, total cholesterol, and LDL-C ↑ FSH, and menstrual regularity; ↓ androgen levels (testosterone & hydroxyprogesterone), anti-Mullerian hormone, and LDL-C

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Pre-surgical anxiety and sedation	3-10 mg, 60-100 minutes prior to standard anesthetic administration in adults	↓ anxiety; ↑ sedation; most effective in combination with alprazolam	B	↑ gamma-aminobutyric acid type A (GABAA) in the CNS
		↓ anxiety; ↑ sedation; no cognitive/psychomotor impairment as seen with midazolam	B	
		↓ anxiety as effectively as gabapentin	B	
		↓ anxiety before, during and after surgery, perioperative pain, fentanyl requirements, and with higher doses intraocular pressure in cataract surgery	B	
	0.1-0.5 mg/kg with/without acetaminophen or paracetamol 45 minutes before anesthetic administration in children	↓ dose of propofol needed for anesthesia than midazolam; as effective as midazolam to induce sedation	B	
		↓ post-operative agitation as effectively as dexmedetomidine and midazolam	B	
		↓ anxiety as effectively as midazolam, post-operative excitement and sleep disturbance 2 weeks post-surgery	C	
Radio-chemotherapy-induced side effects	20 mg per day at night starting 7 days prior to and adjunct with radiotherapy and chemotherapy	↓ risk of asthenia, cachexia, fatigue, hypotension leukopenia, nausea/vomiting, myelosuppression, neurotoxicity, thrombocytopenia	A	↓ TNF, prolactin, IGF-1, & CD4+CD25+ cells ↑ rate of platelet and neutrophil number normalization, and neutrophil apoptosis
Rapid eye movement sleep behavior disorder	3 mg per day 30 minutes before bedtime for 4 weeks in adults	↓ number of 30-s REM sleep epochs without muscle atonia; ↑ CGI score	C	↓ motor activity, number of 30-s REM sleep epochs without muscle atonia

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Sleep disturbance in Alzheimer's disease	2 mg (slow-release) per day, 1-2 hours before bedtime for 24 weeks with standard therapy in the elderly	↑ sleep efficiency, cognitive performance measured by Instrumental Activities of Daily Living (IADL), and Mini-Mental State Examination (MMSE) scores	B	↓ elevation of beta-amyloid, and level of abnormal nitration of proteins in mice ↓ TBARS, and neuronal apoptosis; ↑ SOD and GSH in mice
	3-6 mg (fast-release) per day, 30 minutes to 2 hours before bedtime for 10 days in the elderly with mild cognitive impairment or Alzheimer's type dementia	↑ rest-activity rhythm, sleep quality, and duration; ↓ sleep onset latency, and nocturnal activity May improve ADAS cognition and non-cognition scores	C	
Sleep disturbance in attention deficit hyperactivity disorder	3 mg (<40kg) or 6 mg (>40kg) (fast-release) per day in the evening for 4 weeks in children	↓ time to sleep onset, and dim light melatonin onset; ↑ sleep duration	B	↓ time to sleep onset, dim light melatonin onset
Sleep disturbance in autism spectrum disorder	2-5 mg (slow-release) per day for 10 days and titrated up to 15 mg (if unresponsive) 20-30 minutes before bedtime for up to 3-4 months in children	↓ sleep latency by ~30 minutes; ↑ sleep duration, sleep efficiency with higher doses, clinician and parent impressions of improvement May improve externalizing behaviors	B	Proposed mechanisms: ↑ melatonin levels that may be naturally lower in ASD, ROS scavenging, anti-inflammation, and CD4+ cells which may be lower in ASD, and GABA transmission to reduce overstimulation by excitatory neurotransmitters
Sleep disturbance in cystic fibrosis	3 mg per day, 2 hours before bedtime for 3 weeks in children and young adults	↑ sleep efficiency; ↓ exhaled breath condensate nitrite	C	↓ exhaled breath condensate nitrite

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Sleep disturbance in depression	5-10 mg (slow-release) per day at night for 4 weeks adjunct to fluoxetine in adults	↑ sleep quality	C	Proposed mechanisms: Exogenous melatonin may replace low melatonin levels often observed in major depression that may lead to circadian and sleep disturbances
Sleep disturbance in epilepsy	6 mg (<30 kg; < age of 9) to 9 mg (>30 kg; >age of 9)(fast- or slow-release) as add-on therapy to AEDs within 1 hour of bedtime for 4-8 weeks in children	↓ sleep latency and wakefulness after sleep onset, REM sleep duration, parasomnias score, and total sleep score ↑ slow-wave sleep duration and REM latency	C	Proposed mechanism: ↑ melatonin levels that are reduced in epilepsy, and GABA agonism
Sleep Disturbance in Neuro-developmental Disorders	0.5 mg (fast-release) titrated up to 12 mg over 4 weeks if unresponsive, 45 minutes before bedtime for 12 weeks in children	↑ sleep duration; ↓ sleep onset latency, but may wake up earlier	B	Proposed mechanism: ↑ in melatonin levels that may be compromised in neurodevelopmental disorders to shift circadian rhythms and alter sleep/wake patterns
Sleep disturbance in Parkinson's disease	3-5 mg per day, within 1 hour before bedtime for 1 for 2-4 weeks in adults	↑ sleep quality and quantity; ↓ sleep disturbance, and daytime sleepiness	C	↓ motor activity, number of 30-s REM sleep epochs without muscle atonia
	50 mg per day, 30 minutes before bedtime for 2 weeks in adults	↑ sleep duration	C	↓ COX-2 activity, and levels of nitrates/nitrites and lipoperoxides ↓ oxidation of dopamine in mice
	25 mg twice per day for 1 year in adults	↓ COX-2 activity, levels of nitrates/nitrites and lipoperoxides	C	

Condition	Dosing and administration	Outcome	Class of evidence	MOA
Sleep disturbance in schizophrenia	2-3 mg (slow-release) for 2-3 weeks	↑ sleep efficiency/quality, depth and duration, morning alertness, mood, and daytime functioning; ↓ awakenings, and sleep onset latency	C	Proposed mechanisms: ↑ antioxidative activity as oxidative status is typically higher in schizophrenia, reducing oxidation of dopamine
Sleep disturbance in traumatic brain injury	2 mg (slow-release) per day, 2 hours before bedtime for 4 weeks in adults	↑ sleep quality, efficiency, and scores for vitality and mental health; ↓ scores for anxiety, depression and fatigue	C	↓ rises in oxidative stress seen post-trauma by reducing TBARS, MDA, XO and NO, and increasing brain antioxidants such as GSH or ascorbic acid in rats ↓ neuronal death in rats
Sleep disturbance in tuberous sclerosis	5-10 mg per day, 20 minutes before bedtime for 2 weeks in children	↑ sleep duration Normalizes melatonin patterns in responders Higher doses may continue to improve sleep latency, duration and fragmentation	C	↓ motor activity, number of 30-s REM sleep epochs without muscle atonia ↑ level of sedation
Temporo-mandibular disorders	5 mg per day at bedtime for 4 weeks in adults	↓ pain scores, and use of other analgesics; ↑ pain threshold	C	↑ pain threshold ↓ BDNF levels

For an explanation of the classes of evidence, please see the Rating Scales for Evidence-Based Decision Support.

Adverse Effects

Melatonin is generally considered safe with short-term oral administration, even with large doses of up to 3.5 mg. However, it is not recommended to take melatonin if pregnant or breast-feeding. The most common adverse effects are considered mild and may include dizziness, headaches, nausea, sleepiness, or hypothermia. Most cases are resolved within a few days or upon discontinuation. Rare cases of agitation, fatigue, mood swings, nightmares, skin irritation, and heart palpitations have been reported.

Associated interactions

Melatonin is primarily metabolized in the liver by CYP1A2, with smaller metabolic activity from CYP2C19 and CYP2C9. Some metabolism may occur in the intestines or skin by CYP1A1 and CYP1B1. Melatonin may interact with certain nutrients, herbs, and pharmaceuticals that follow similar metabolic pathways.

Class of drug/nutrient	Pharmaceutical	Effect	Class of evidence
ACE inhibitors	Capozide-50	Combination with melatonin (3 mg) further reduces SBP, DBP, and MAP than pharmaceutical alone	D
Anaesthetics	Propofol	Reduces required dose to induce anesthesia in adults	B
	Thiopental	Reduces required dose to induce anesthesia in adults	B
Angiotensin receptor blockers	Losartan	Combination with melatonin (3 mg) further reduces BP, cardiac output, myocardium energy use; normalizes chrono structure of BP and HR of circadian rhythms	D
Anti-anemics	Iron and erythropoietin	Melatonin (18 mg) reduces treatment-associated oxidative stress via prevention of increases in MDA, and CAT activity, and decreases in hemoglobin GSH	D
Anti-coagulants	Warfarin	Melatonin may potentiate warfarin and may independently lower fibrinogen or coagulation factor VII	A
Anti-convulsants	Gabapentin	Melatonin (3 mg per day) can reduce gabapentin's daytime sleepiness side-effects	B
Benzodiazepines	Alprazolam	The combination reduced anxiety more than placebo, melatonin (3 mg per day) or pharmaceutical alone	B
Biguanides	Metformin	Combination with melatonin (10 mg) and zinc acetate (50 mg) improves tissue responses to metformin for fasting and postprandial glycemic control, as well as improves impaired lipid profile and reduced MAU status	C
Calcium channel blockers	Nifedipine	Combination with melatonin (5 mg) increases SBP, DBP, and HR, possibly through competitive interference	C

Class of drug/nutrient	Pharmaceutical	Effect	Class of evidence
Chemotherapeutics	Cisplatin and etoposide	Melatonin (1 mg per day) may reduce chemo-induced anemia	D
	Epirubicin	Melatonin (20 mg per day) may prevent chemo-induced reductions in platelets	D
CNS stimulants	Caffeine	Melatonin (6 mg) has higher bioavailability with concomitant caffeine via inhibited CYP1A2, and caffeine alone can raise melatonin levels. These effects may be observed particularly within 24 hours of caffeine ingestion.	C
Contraceptives (oral)	-	Melatonin (6 mg) combination increases serum melatonin and reduces clearance via CYP1A2 inhibition with contraceptives	D
Herbals	St. John's wort	Increases melatonin levels	C
	Vitex agnus-castus	Increases melatonin secretion	C
Proton pump inhibitors	Lansoprazole	Increases melatonin levels possibly via reduced CYP2C19 activity	C
	Omeprazole	Increases melatonin levels possibly via reduced CYP2C19 activity; melatonin (5 mg b.i.d) improves gastroduodenal ulcers healing compared to drug alone	C
Second-generation antipsychotics	Clozapine, olanzapine, quetiapine, or risperidone	Melatonin attenuates metabolic side effects by preventing rises in DBP or SBP, weight gain, fat mass, or total cholesterol	C
Sedative	Zolpidem	Melatonin (2 mg) combination further impairs psychomotor, memory, and driving performance	C
Selective serotonin reuptake inhibitors	Citalopram	Increases melatonin levels possibly via reduced CYP2C19 activity	C
	Fluvoxamine	Increases melatonin levels possibly via reduced CYP1A2 and/or CYP2C19	C
Tricyclic antidepressants	Desipramine	Increases evening melatonin and evening/morning cortisol concentrations	D

Associated depletions

Class of drug	Pharmaceutical/ ingredient	Effect	Class of evidence
Alcohol	Ethanol (1g/kg)	↑ nocturnal norepinephrine; ↓ nocturnal melatonin secretion; Secretion is also suppressed when consuming wine that does not contain natural melatonin	C
Analgesics	Morphine (40 kg/m2)	↓ intraoperative and postoperative melatonin secretion	D
Benzodiazepines	Alprazolam (2 mg)	↓ nocturnal melatonin & cortisol	D
	Diazepam (10 mg)	↓ nocturnal melatonin	C
	Flunitrazepam (1 mg)	↓ nocturnal melatonin	C
Beta-blockers	Bisoprolol (10 mg)	↓ nocturnal melatonin synthesis	C
	Metoprolol (100-400 mg)	↓ melatonin synthesis	C
	Ridazolol	↓ nocturnal melatonin synthesis by 50%	D
	(S)-atenolol (50 mg)	↓ nocturnal melatonin synthesis by 86% in a dose-dependent manner	C
	(S)-propranolol (10-40 mg)	↓ nocturnal melatonin synthesis by 50-80%, and with exercise-induced oxidative stress	C
Calcium channel blockers	Verapamil (240 mg)	↑ nocturnal melatonin excretion by 67-145%	C
NSAIDs	Aspirin	↓ nocturnal melatonin synthesis	B
	Ibuprofen (400 mg)	↓ nocturnal melatonin synthesis and delays release	B
	Indomethacin (75 mg)	Inhibits melatonin release	D
Selective serotonin reuptake inhibitor (SSRI)	Citalopram (30 mg)	↓ melatonin synthesis by 47% and delays release	C
	Fluoxetine (20-40 mg)	↓ nocturnal melatonin synthesis	D
Vitamins	B12 (methylcobalamin or cyanocobalamin) (3 mg)	↓ 24-h melatonin, nocturnal melatonin with light exposure; phase-advances the circadian rhythm	C

Pharmacokinetics

Absorption: The oral bioavailability of melatonin is approximately 15%. In healthy individuals, administration of oral immediate-release formulations results in maximum plasma concentrations after approximately 45 minutes. Slow-release formulations prolong this effect to approximately 2 hours and 45 minutes. Sublingual preparations are absorbed at a rate comparable to oral formulations but result in higher maximal plasma concentrations by bypassing first pass metabolism.

Distribution: Melatonin is both lipid- and water-soluble, and can readily cross the blood-brain barrier. Melatonin receptors (ML1) and (ML2) are located broadly across central and peripheral tissues in humans. The ML1 subtype MT1 is found particularly in the anterior pituitary and the suprachiasmatic nuclei of the hypothalamus, while the ML1-MT2 subtype is found primarily in the retina. ML2 (currently known as MT3) receptors are distributed throughout the brain. Melatonin receptors are also located in cardiovascular tissues, T and B lymphocytes, and adipocytes, as well as in the adrenal glands, kidneys, lungs, liver, gallbladder, small intestine, ovaries, uterus, breasts, prostate, and skin.

Metabolism: Extensive first-pass metabolism likely contributes to melatonin's low oral bioavailability, particularly due to its high affinity to CYP1A2. The half-life of oral immediate-release formulations is approximately 45 minutes, while the half-life of slow-release formulation is one and a half hours. Melatonin can be produced and metabolized in the skin by CYP1B1.

Excretion: Melatonin is excreted in the urine. Most melatonin is excreted in its sulfurated- (~90%) or glucuronidated-forms (~10%), though up to 5% may be expelled in its unmetabolized form. The primary metabolite, 6-sulfatoxy-melatonin (6-SM), can be used as a measure of plasma melatonin levels.