CLINICAL MONOGRAPH · SLEEP & RECOVERY

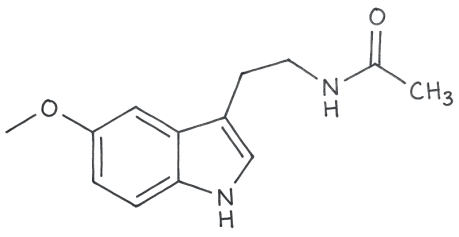
Compounded Melatonin

Sleep-cycle hormone in custom strengths and delivery forms

Melatonin is a hormone the brain makes at night to tell the body that it is time to sleep. The pineal gland releases it on a roughly 24-hour cycle controlled by a master clock in the brain called the suprachiasmatic nucleus [aulinas2019]. Light suppresses melatonin; darkness allows it to rise.

Taken as a medicine, melatonin is most useful for resetting the body clock, for jet lag, delayed sleep-wake phase disorder (a problem mostly in teenagers and young adults where the body cannot fall asleep until very late), shift-work-related sleep disturbance, and insomnia in children with autism spectrum disorder [auger2015; gringras2017; auld2017]. It is less reliable for ordinary adult insomnia, where it shortens the time to fall asleep by only a small amount on average.

In the United States melatonin is sold over the counter as a dietary supplement, not as an FDA-approved drug. Independent testing has shown that OTC products often contain very different amounts of melatonin than the label states [erland2017]. A compounded melatonin preparation is dispensed by a pharmacy on a prescription so that the strength, the dose form (such as a sublingual or a slow-release capsule), and the inactive ingredients can be matched to a specific patient's clinical needs [herxheimer2002].



EVIDENCE POSTURE EMERGING WELL STUDIED REVIEWED **2026-05-11**


State-licensed 503A


Pharmacist reviewed


Doctor led


Cold-chain ready


Patient choice preserved

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FOR CLINICIANS

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous pineal indoleamine synthesized from tryptophan via serotonin under suprachiasmatic-nucleus (SCN) control [aulinas2019]. Endogenous secretion rises after dim-light melatonin onset (DLMO), peaks in the middle of the biological night, and is acutely suppressed by light exposure. Exogenous melatonin acts at MT1 and MT2 G-protein-coupled receptors expressed in the SCN, retina, and pars tuberalis [reppert1995_mt1; reppert1995_mt2; weaver1996]. Therapeutic effects are best understood as two distinct actions: a chronobiotic (phase-shifting) action governed by a low-dose, timed phase response curve [burgess2010, lewy1997], and a milder hypnotic action requiring higher doses that elevate plasma melatonin above physiologic peak [ema_circadin].

Evidence is strongest for circadian rhythm sleep-wake disorders. The 2015 AASM clinical practice guideline [auger2015] supports timed melatonin for delayed sleep-wake phase disorder (DSWPD) and non-24-hour sleep-wake rhythm disorder [dubocovich2007]. A double-blind RCT [sletten2018] confirmed efficacy of low-dose melatonin combined with behavioral sleep-wake scheduling in DSWPD. The Cochrane review of melatonin for jet lag [herxheimer2002] reported substantial benefit when timed appropriately, particularly after eastward travel across multiple time zones. For shift-work-related sleep disturbance the Cochrane review [liira2014] reported small improvements in daytime sleep duration. For pediatric insomnia in autism spectrum disorder, a phase 3 trial of pediatric prolonged-release melatonin [gringras2017] and earlier dose-finding work [malow2012, goldman2014] support clinically meaningful improvements in sleep onset and duration with acceptable tolerability [ema_circadin].

For primary adult insomnia, meta-analyses [brzezinski2005, buscemi2005, auld2017] report a small but reproducible reduction in sleep onset latency (on the order of 7, 12 minutes) and limited effect on total sleep time. The EMA-approved prolonged-release product (Circadin 2 mg) is indicated for short-term primary insomnia in adults aged 55 and older [ema_circadin] [wade2007; wade2010]. The EMA-approved pediatric prolonged-release product (Slenyto) is indicated for insomnia in children with autism spectrum disorder following Gringras 2017 [gringras2017, ema_slenyto] [lemoine2012]. In the United States there is no FDA-approved melatonin drug product; OTC supplements are regulated under DSHEA [fda_dshea]. Independent assay of OTC products [erland2017] demonstrated melatonin content ranging from approximately −83% to +478% of label claim and detection of serotonin contamination in a subset of products, motivating compounded preparation when documented strength, identity, and excipient control are clinically necessary [liu1997; wade2011].

Safety is generally favorable in short-term controlled trials and meta-analyses [andersen2016_safety, besag2019]. Adverse events are typically mild (headache, daytime sleepiness, dizziness, nausea). CYP1A2 is the principal metabolizing enzyme; potent CYP1A2 inhibitors such as fluvoxamine markedly raise oral melatonin exposure [hartter2000] [ema_circadin]. Pregnancy, lactation, and long-term pediatric use have limited controlled data; use in pregnancy is generally avoided outside specific research contexts. Pediatric unsupervised ingestion has risen sharply in the US [lelak2022], reinforcing the need for child-resistant packaging and dose individualization when a compounded product is appropriate.

Why Personalized Compounded Melatonin

The melatonin doses studied in the published trials were not chosen for you. The chronobiotic effect runs on 0.1 to 0.5 mg timed to your own dim-light melatonin onset; the milder hypnotic effect on sleep onset latency runs on higher milligram doses near bedtime. Those are two different drugs in one molecule, and the right one depends on whether your problem is a body clock that fires too late, jet lag after an eastward flight, a child with autism who cannot stay asleep, or ordinary adult insomnia. The studies also did not account for whether you take fluvoxamine, which raises oral melatonin exposure roughly seventeen-fold, or whether the OTC bottle you picked off the shelf actually contains what the label says.

That gap is the work a compounding pharmacy does. A prescribing clinician can write 0.3 mg for a teenager with delayed sleep-wake phase disorder when the OTC shelf starts at 1 mg, switch to a sublingual fast-dissolve when first-pass metabolism is blunting the response, prepare a prolonged-release capsule sized to the patient's actual sleep window, and remove the dyes, gelatin, lactose, or flavorings in the OTC chewable a child with autism cannot tolerate. Every capsule is weighed gravimetrically and the batch is identity- and strength-verified before it leaves the pharmacy, which is the part the OTC supplement supply does not do. Independent assays of OTC melatonin have found wide deviation from label content, including pediatric products. Compounding closes that loop on a named patient.

This is what pharmacy looked like before mass manufacturing arrived. A clinician wrote the prescription. A pharmacist prepared it for that patient. Compounded melatonin is that older arrangement, kept honest by modern oversight.

Quick Facts About Compounded Melatonin

Category: Endogenous pineal indoleamine; MT1/MT2 receptor agonist

Active ingredient: N-acetyl-5-methoxytryptamine (melatonin), a tryptophan-derived indoleamine secreted by the pineal gland under suprachiasmatic-nucleus control

U.S. regulatory status: Sold over the counter as a dietary supplement under DSHEA; there is no FDA-approved melatonin drug product in the United States

EU regulatory status: Prolonged-release melatonin 2 mg (Circadin) is approved by the EMA for short-term primary insomnia in adults aged 55 and older; pediatric prolonged-release melatonin (Slenyto) was approved by the EMA in 2018 for insomnia in children with autism spectrum disorder

Common routes: Oral immediate-release, oral prolonged-release, sublingual fast-dissolve, troche

Evidence posture: Well-studied for circadian rhythm sleep-wake disorders (DSWPD, jet lag, shift-work-related sleep disturbance) and pediatric ASD-related insomnia; emerging for migraine prophylaxis, oncology adjunct, headache, and other indications

Compounded under: 503A, patient-specific prescription, used when OTC supplement strength, purity, dosage form, or excipient profile cannot meet a documented clinical need

Important note: Commercial OTC melatonin products show wide variation in actual versus labeled melatonin content and have been associated with rising pediatric ingestions; compounded preparations provide documented strength, identity, and excipient control on a per-batch basis

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Compounded Melatonin described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Compounded Melatonin?

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine hormone synthesized in the pineal gland from tryptophan via the intermediates serotonin and N-acetylserotonin. The pineal gland is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, which itself is entrained primarily by light input from intrinsically photosensitive retinal ganglion cells through the retinohypothalamic tract [aulinas2019].

Melatonin secretion rises in the evening, peaks in the middle of the biological night, and is acutely suppressed by light, particularly short-wavelength (blue) light.

Melatonin was first isolated and identified by Aaron Lerner and colleagues at Yale in 1958 from bovine pineal extracts on the basis of its skin-lightening effect on amphibian melanocytes. The MT1 and MT2 receptors that mediate most central effects were cloned in 1994, 1995 [reppert1995_mt1, reppert1995_mt2]. The molecule is small (MW 232), lipophilic, and crosses the blood-brain and placental barriers.

As a pharmaceutical substance, melatonin is available globally in several regulatory categories: an OTC dietary supplement in the United States under the Dietary Supplement Health and Education Act (DSHEA) [fda_dshea]; an EMA-approved prolonged-release prescription drug (Circadin 2 mg) for primary insomnia in adults aged 55 and older [ema_circadin]; an EMA-approved pediatric prolonged-release product (Slenyto) for insomnia in children with autism spectrum disorder [ema_slenyto]; and a 503A-compounded preparation in the United States when patient-specific factors call for a strength, dosage form, or excipient profile that the OTC supply cannot provide. Compounded preparations are dispensed only on patient-specific prescription.

How Compounded Melatonin Works

Melatonin acts primarily through two high-affinity G-protein-coupled receptors, MT1 and MT2, expressed at highest density in the SCN and retina and at lower density across many tissues [reppert1995_mt1; reppert1995_mt2]. Both receptors couple to Gαi, lowering intracellular cAMP, and to additional signaling cascades. MT1 activation in the SCN acutely suppresses neuronal firing and contributes to the hypnotic/sedative profile observed at supra-physiologic plasma concentrations; MT2 activation drives the phase-shifting (chronobiotic) effect that adjusts the timing of the circadian system.

Two clinically distinct actions follow from this receptor pharmacology [liu1997]. The chronobiotic action is the phase shift produced by exogenous melatonin given at low doses (typically 0.3, 0.5 mg) at a time outside the endogenous melatonin window: doses given in the early evening produce a phase advance (earlier sleep timing) and doses given in the late biological night produce a phase delay [lewy1997, burgess2010] [dubocovich2007]. The hypnotic action is a milder direct sleep-promoting effect that requires immediate-release oral doses sufficient to elevate plasma melatonin well above its physiologic peak.

Beyond MT1/MT2 signaling, melatonin and several of its metabolites have direct radical-scavenging and indirect antioxidant activity in vitro and in animal models [pandi2013, hardeland2012]. The clinical relevance of these antioxidant effects in humans at oral supplemental doses is less well established than the receptor-mediated circadian effects.

Biological Role of Compounded Melatonin

Endogenous melatonin is the principal hormonal output of the circadian system. Its nighttime rise communicates the timing of the biological night to peripheral tissues, including pancreatic islets, adipose tissue, vascular endothelium, and reproductive tissues, all of which express MT1 and/or MT2 receptors. Endogenous melatonin amplitude declines with age, particularly after the seventh decade, and is reduced in shift workers, in people with prolonged light exposure during the biological night, and in some neurodegenerative conditions [aulinas2019, lemoine2012].

From a chronobiotic standpoint, melatonin and bright light are complementary entrainment signals: bright light in the early biological morning advances phase; bright light in the late biological evening delays it; exogenous melatonin in the late biological afternoon-early evening advances phase; exogenous melatonin in the late biological night delays it [burgess2010, lewy1997]. The clinical use of melatonin for delayed sleep-wake phase disorder, jet lag, and shift-work-related sleep disturbance follows from this physiology rather than from a direct hypnotic effect.

Detailed Mechanism of Compounded Melatonin

Endogenous melatonin biosynthesis begins with tryptophan, proceeds through serotonin and N-acetylserotonin (with arylalkylamine N-acetyltransferase as the rate-limiting enzyme), and ends with O-methylation by hydroxyindole-O-methyltransferase. The SCN drives the diurnal rhythm of N-acetyltransferase activity through a multi-synaptic pathway via the paraventricular nucleus, intermediolateral cell column, and superior cervical ganglion to the pineal gland [aulinas2019]. Light incident on intrinsically photosensitive retinal ganglion cells signals through the retinohypothalamic tract to the SCN and acutely suppresses pineal melatonin secretion [reppert1995_mt1].

Plasma melatonin rises starting approximately 2 hours before habitual sleep onset; the time at which it exceeds a threshold (typically 3, 10 pg/mL in saliva, or higher in plasma) is the dim-light melatonin onset (DLMO), the most widely used physiologic marker of internal circadian phase. DLMO is used to time exogenous melatonin administration in clinical trials of circadian rhythm sleep-wake disorders [auger2015, sletten2018] [dubocovich2007]. The phase response curve (PRC) for exogenous melatonin in humans, characterized at 0.5 mg and 3.0 mg doses, demonstrates phase advances of approximately 1, 1.5 hours per day when melatonin is given several hours before DLMO and phase delays when given in the late biological night [burgess2010, lewy1997]. The 0.5 mg dose produced phase shifts indistinguishable from the 3.0 mg dose in healthy adults, supporting the use of low (sub-mg to 0.5 mg) doses for chronobiotic indications.

MT1 and MT2 receptors differ in tissue distribution, signaling bias, and pharmacology. MT1 is expressed prominently in the SCN, where its activation suppresses neuronal firing in vitro [liu1997] and contributes to the acute sleep-promoting effect of melatonin. MT2 is more widely expressed in the SCN and retina and

mediates the phase-shifting action. Selective MT1/MT2 agonists (ramelteon, tasimelteon, agomelatine, the last with additional 5-HT2C antagonism) have been developed as approved drugs in non-US markets and, for ramelteon and tasimelteon, in the US (separate FDA approvals), but those are distinct molecular entities from melatonin itself and are out of scope for this brief [reppert1995_mt1; reppert1995_mt2].

Melatonin also exhibits direct radical-scavenging activity against hydroxyl radical, peroxyl radical, peroxynitrite, and singlet oxygen, and indirect antioxidant effects through upregulation of antioxidant enzymes [pandi2013; hardeland2012] [reppert1995_mt1]. Several oxidative metabolites (cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykynuramine, N1-acetyl-5-methoxykynuramine) retain antioxidant activity, producing an antioxidant cascade. These actions are receptor-independent and operate at doses well above physiologic exposure.

Compounded Melatonin Research History

Melatonin was isolated by Aaron Lerner and colleagues at Yale in 1958 from bovine pineal extracts on the basis of its skin-lightening (melanocyte-aggregating) action in amphibians; the name reflects this discovery context. Subsequent work through the 1960s and 1970s by Wurtman, Axelrod, and others established the diurnal rhythm of pineal N-acetyltransferase activity and the SCN-pineal axis [aulinas2019]. The MT1 (Mel1a) and MT2 (Mel1b) receptors were cloned by Reppert and colleagues in 1994, 1995 [reppert1995_mt1, reppert1995_mt2] and the Mel1a expression in the human SCN was confirmed shortly after [weaver1996, liu1997]. Receptor pharmacology was reviewed by Dubocovich in 2007 [dubocovich2007].

Clinical chronobiology of exogenous melatonin was advanced through the 1990s and 2000s by Lewy, Sack, Eastman, Burgess, and others, who characterized the human phase response curve to exogenous melatonin [lewy1997, burgess2010]. Cochrane reviews of melatonin for jet lag [herxheimer2002] and shift work [liira2014] consolidated the chronobiotic evidence. The AASM published its first clinical practice guideline on intrinsic circadian rhythm sleep-wake disorders in 2007 and an update in 2015 [auger2015], with conditional recommendations for timed melatonin in delayed sleep-wake phase disorder.

Evidence for primary adult insomnia accumulated through several meta-analyses [brzezinski2005, buscemi2005, auld2017], with consistent findings of small reductions in sleep onset latency. Prolonged-release melatonin 2 mg (Circadin) received EMA approval in 2007 for short-term primary insomnia in adults aged 55 and older following trials by Wade and colleagues [wade2007; wade2010; wade2011]. A US FDA approval was not pursued. Pediatric prolonged-release melatonin (Slenyto) was approved by the EMA in 2018 for insomnia in children with autism spectrum disorder on the basis of the Gringras et al [lemoine2012]. phase 3 trial [gringras2017, ema_slenyto]. Earlier dose-finding work in pediatric ASD [malow2012, goldman2014] supported the dosing strategy. A randomized controlled trial of melatonin for migraine prophylaxis [goncalves2016] reported non-inferiority versus amitriptyline 25 mg with superior tolerability. A systematic review and meta-analysis of melatonin as an oncology adjunct [mills2005]

reported preliminary effects on one-year survival across solid tumors but the underlying trials are largely from a single research group, and a later systematic review [seely2012] extended the analysis with similar caveats.

Concerns about OTC supplement quality and unsupervised pediatric ingestion have driven the contemporary 503A framing. Independent assay of OTC melatonin products [erland2017] documented wide deviation from label claim, and a CDC MMWR analysis of US Poison Control reports documented a five-fold rise in pediatric melatonin ingestions across 2012, 2021, with a sharp acceleration during the COVID-19 pandemic [lelak2022].

Compounded Melatonin Timeline

- **1958** • Lerner and colleagues at Yale isolate melatonin from bovine pineal extracts and name it for its melanocyte-aggregating action in amphibians [aulinas2019]
- **1995** • Reppert et al [reppert1995_mt1; reppert1995_mt2]. clone the MT1 (Mel1a) melatonin receptor in Neuron and the MT2 (Mel1b) melatonin receptor in PNAS, establishing the molecular basis for chronobiotic and hypnotic effects
- **1996** • Weaver and Reppert confirm Mel1a (MT1) receptor expression in the human suprachiasmatic nucleus [weaver1996]
- **1997** • Liu et al [liu1997]. (Neuron) dissect the two distinct actions of melatonin on the suprachiasmatic circadian clock, acute firing suppression and circadian phase shift
- **1997** • Lewy et al [lewy1997]. characterize the phase-shifting effect of exogenous melatonin on the endogenous melatonin profile in sighted humans
- **2000** • Härtter et al [hartter2000]. (Clin Pharmacol Ther) demonstrate that fluvoxamine markedly increases oral melatonin bioavailability, establishing CYP1A2 as the principal metabolizing pathway
- **2002** • Herxheimer and Petrie publish the Cochrane review of melatonin for the prevention and treatment of jet lag [herxheimer2002]
- **2005** • Brzezinski et al [brzezinski2005]. (Sleep Med Rev) meta-analysis on effects of exogenous melatonin on sleep, modest reductions in sleep onset latency and increases in sleep efficiency
- **2005** • Buscemi et al [buscemi2005]. (J Gen Intern Med) meta-analysis on melatonin for primary sleep disorders, reductions in sleep onset latency of approximately 7 minutes
- **2005** • Mills et al [mills2005]. (J Pineal Res) systematic review and meta-analysis of melatonin in the treatment of cancer, preliminary signal on one-year survival

- **2006** • Buscemi et al [buscemi2006]. (BMJ) meta-analysis on melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction
- **2007** • Dubocovich (Sleep Medicine) reviews melatonin receptor pharmacology and its role in sleep and circadian regulation [dubocovich2007]
- **2007** • EMA approves Circadin (prolonged-release melatonin 2 mg) for short-term primary insomnia in adults aged 55 and older, first regulatory drug approval of melatonin [ema_circadin; wade2007]
- **2010** • Burgess et al [burgess2010]. (J Clin Endocrinol Metab) publish the human phase response curve to three days of daily melatonin at 0.5 mg vs 3.0 mg, demonstrating that low doses produce phase shifts comparable to higher doses
- **2010** • Wade et al [wade2010]. (BMC Medicine) report a 6-month randomized placebo-controlled trial of prolonged-release melatonin for primary insomnia, examining age and endogenous melatonin as moderators
- **2011** • Wade et al [wade2011]. (Curr Med Res Opin) further analyze the age cut-off for short- and long-term efficacy of prolonged-release melatonin in primary insomnia
- **2012** • Malow et al [malow2012]. (J Autism Dev Disord) report a controlled dose-finding trial of melatonin for sleep in children with autism spectrum disorder
- **2012** • Seely et al [seely2012]. (Integr Cancer Ther) systematic review and meta-analysis of melatonin as adjuvant cancer care with and without chemotherapy
- **2012** • Lemoine and Zisapel (Expert Opin Pharmacother) review prolonged-release melatonin (Circadin) for the treatment of insomnia [lemoine2012]
- **2014** • Liira et al [liira2014]. publish the Cochrane review of pharmacological interventions including melatonin for sleepiness and sleep disturbances caused by shift work
- **2014** • Goldman et al [goldman2014]. (J Autism Dev Disord) characterize endogenous and pharmacokinetic melatonin profiles in children with autism spectrum disorder
- **2015** • AASM clinical practice guideline (Auger et al., J Clin Sleep Med) for intrinsic circadian rhythm sleep-wake disorders, conditional recommendations for timed melatonin in DSWPD and N24SWD [auger2015]
- **2015** • Harpsøe et al [harpsoe2015]. (Eur J Clin Pharmacol) systematic review of the clinical pharmacokinetics of melatonin
- **2016** • Gonçalves et al [goncalves2016]. (J Neurol Neurosurg Psychiatry) randomized clinical trial comparing melatonin 3 mg, amitriptyline 25 mg, and placebo for migraine prevention, melatonin superior to placebo and non-inferior to amitriptyline with better tolerability

- **2016** • Andersen et al [andersen2016_safety]. (Clin Drug Investig) review the safety of melatonin in humans
- **2017** • Erland and Saxena (J Clin Sleep Med) assay 31 commercial OTC melatonin products, content ranges from −83% to +478% of label and serotonin contamination is identified in a subset [erland2017]
- **2017** • Gringras et al [gringras2017]. (J Am Acad Child Adolesc Psychiatry) publish the phase 3 trial of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder, basis for the EMA Slenyto approval
- **2017** • Auld et al [auld2017]. (Sleep Med Rev) systematic review of melatonin for primary adult sleep disorders consolidates the small but reproducible effect on sleep onset latency
- **2018** • Sletten et al [sletten2018]. (PLoS Medicine) double-blind randomized trial of low-dose melatonin combined with behavioral sleep-wake scheduling for delayed sleep-wake phase disorder
- **2018** • EMA approves Slenyto (pediatric prolonged-release melatonin) for insomnia in children with autism spectrum disorder [ema_slenyto]
- **2019** • Besag et al [besag2019]. (CNS Drugs) systematic review of adverse events associated with melatonin for primary or secondary sleep disorders
- **2019** • Aulinas (Endotext) updates the comprehensive review of pineal gland physiology and melatonin [aulinas2019]
- **2021** • Lalanne et al [lalanne2021]. (Int J Mol Sci) review melatonin pharmacokinetics and clinical use in autism spectrum disorder
- **2022** • Lelak et al [lelak2022]. (CDC MMWR) report a five-fold rise in pediatric melatonin ingestions in the United States across 2012, 2021, with a marked pandemic-era acceleration

Clinical Contexts for Compounded Melatonin

Delayed sleep-wake phase disorder (DSWPD) WELL STUDIED

Conditionally recommended by the AASM 2015 guideline; supported by a double-blind randomized trial. Not an FDA-approved indication in the United States.

The 2015 AASM clinical practice guideline for intrinsic circadian rhythm sleep-wake disorders [auger2015] issued a conditional recommendation for timed strategic melatonin in adults with delayed sleep-wake phase disorder. The Sletten 2018 PLoS Medicine RCT [sletten2018] demonstrated that low-dose melatonin (0.5 mg) given approximately 1 hour before the desired bedtime, combined with behavioral sleep-wake scheduling, produced clinically meaningful advances in sleep timing relative to placebo in adults with DSWPD. Earlier human phase response curve work [lewy1997, burgess2010] provided the pharmacologic basis. Dosing is timed by reference to the individual's dim-light melatonin onset (DLMO) when feasible.

Jet lag WELL STUDIED

Well studied across multiple controlled trials and a Cochrane review.

The Cochrane review by Herxheimer and Petrie [herxheimer2002] pooled 10 randomized trials of melatonin for jet lag and reported substantial reduction in jet-lag symptom severity after travel across five or more time zones, particularly eastward. Effective doses were 0.5, 5 mg taken near bedtime at the destination for several days. Higher doses were not consistently more effective than 0.5 mg; immediate-release preparations were generally superior to slow-release for this indication.

Shift-work-related sleep disturbance WELL STUDIED

Modest effect on daytime sleep duration; supported by a Cochrane review.

The Cochrane review by Liira et al. [liira2014] of pharmacological interventions for shift-work-related sleepiness and sleep disturbance reported that melatonin taken at bedtime after a night shift increased daytime sleep duration by approximately 24 minutes versus placebo across pooled trials, without significant improvement in subjective sleep quality or wakefulness during night shifts.

Insomnia in children with autism spectrum disorder WELL STUDIED

Phase 3 evidence supports pediatric prolonged-release melatonin (Slenyto); EMA-approved in the EU and not FDA-approved in the United States.

The Gringras et al. phase 3 trial [gringras2017] randomized 125 children aged 2, 17.5 years with autism spectrum disorder and chronic insomnia to pediatric prolonged-release melatonin 2 mg titrated to 5 mg or placebo for 13 weeks [lalanne2021]. Sleep latency, total sleep time, and longest sleep episode improved significantly with melatonin versus placebo, with acceptable tolerability. Earlier dose-finding work in pediatric ASD [malow2012] reported similar efficacy across 1, 3, and 6 mg doses. Endogenous and pharmacokinetic profiles in pediatric ASD have been characterized [goldman2014]. The European Medicines Agency approved pediatric prolonged-release melatonin (Slenyto) in 2018 for this indication [ema_slenyto]. The US has no FDA-approved pediatric melatonin drug product.

Primary insomnia in adults aged 55 and older WELL STUDIED

EMA-approved indication for the prolonged-release prescription product Circadin (2 mg) in the EU. Not an FDA-approved indication in the United States.

Wade et al. [wade2007] reported improved sleep quality and morning alertness with prolonged-release melatonin 2 mg in adults aged 55 and older. A 6-month placebo-controlled trial [wade2010] demonstrated sustained efficacy and tolerability and identified age and baseline endogenous melatonin as moderators of response. A pooled analysis [wade2011] supported a 55-year age cut-off for the indication. Lemoine and Zisapel [lemoine2012] reviewed the prolonged-release product in detail. The European Medicines Agency approved Circadin 2 mg [ema_circadin] for short-term primary insomnia in adults aged 55 and older. The United States has no FDA-approved melatonin product for any insomnia indication.

Migraine prophylaxis EMERGING

Supported by a randomized non-inferiority trial vs amitriptyline; not an FDA-approved indication.

Gonçalves et al. [goncalves2016] randomized 196 adults with episodic migraine to melatonin 3 mg, amitriptyline 25 mg, or placebo over 3 months. Both active arms reduced headache frequency more than placebo; melatonin was non-inferior to amitriptyline and produced fewer adverse events (weight loss vs weight gain, fewer anticholinergic complaints). Mechanistic hypotheses link low endogenous melatonin to migraine pathophysiology, but additional adequately powered trials are needed before melatonin is considered a first-line prophylactic agent.

Primary insomnia (general adult population) WELL STUDIED

Small reductions in sleep onset latency in meta-analyses; not recommended as first-line therapy by major US sleep guidelines for chronic insomnia.

Meta-analyses of melatonin for primary adult insomnia [brzezinski2005, buscemi2005, auld2017] consistently report small reductions in sleep onset latency (approximately 7, 12 minutes pooled) and limited effects on total sleep time. The Buscemi BMJ analysis of secondary sleep disorders [buscemi2006] found no significant effect on sleep parameters in adults with sleep disorders secondary to other conditions. Effect sizes are modest compared with established pharmacotherapy and with cognitive behavioral therapy for insomnia; the US AASM and ACP guidelines do not recommend melatonin as a primary chronic-insomnia therapy in adults under 55.

Oncology adjunct EMERGING

Preliminary evidence from systematic reviews; underlying trials are concentrated in a single research group and the indication is investigational.

A systematic review and meta-analysis of randomized trials [mills2005] reported reductions in one-year mortality and treatment-related toxicity when melatonin was added to standard oncology care across solid tumors. A subsequent broader systematic review with and without chemotherapy [seely2012] reached qualitatively similar conclusions. A substantial fraction of the underlying trials originated from a single Italian research group and many trials had methodologic limitations, limiting generalizability. Melatonin should not be recommended as an oncology adjunct outside the context of a clinical trial or specialist oncologic care.

Off-Label Uses of Compounded Melatonin

Headache and migraine prophylaxis (outside the Gonçalves 2016 protocol) EMERGING

Emerging, single adequately powered RCT and supportive observational data.

Outside the Gonçalves 2016 randomized trial protocol [goncalves2016] (3 mg 30 minutes before bedtime for 3 months), broader off-label use of melatonin for migraine prophylaxis and other headache disorders is supported only by smaller open-label series and observational data.

Antioxidant or general wellness use EMERGING

Preclinical and mechanistic rationale only; not supported as a clinical indication.

Melatonin has direct radical-scavenging activity in vitro and in animal models [pandi2013, hardeland2012]. Translation to clinical antioxidant benefit at oral supplemental doses in healthy adults is not established. Use as a general antioxidant is not a supported clinical indication.

Compounded Compounded Melatonin (503A)

Melatonin is sold over the counter as a dietary supplement in the United States under DSHEA; there is no FDA-approved melatonin drug product on the US market [fda_dshea] [fda503a]. Compounded melatonin under 503A is dispensed on a patient-specific prescription when the prescribing clinician documents a clinical need that the OTC supply cannot meet. Documented needs typically fall into four categories: (1) custom strength outside commercially available OTC dose increments, particularly low strengths of 0.1, 0.5 mg used for chronobiotic indications, where the OTC supply concentrates on 1, 3, 5, and 10 mg adult-marketed strengths and where independent assay of OTC products has documented substantial deviation from label claim [erland2017]; (2) dosage form not commercially available, for example sublingual fast-dissolve at custom strengths for rapid onset before bedtime in adults with circadian phase disturbance, or a compounded prolonged-release oral capsule modeled on the EMA-approved profile [ema_circadin, lemoine2012]; (3) excipient sensitivity or allergen avoidance (gluten, lactose, gelatin, dyes, common flavoring agents in OTC chewables); and (4) pediatric dose individualization, particularly in autism spectrum disorder where the published evidence supports 2, 5 mg of pediatric prolonged-release [gringras2017] but where OTC pediatric products are not standardized and have been associated with marked deviation from label content [erland2017].

Pharmaceutical-grade purity is a distinguishing feature of 503A-compounded melatonin relative to the OTC dietary supplement supply. The Erland and Saxena 2017 J Clin Sleep Med assay [erland2017] of 31 commercial OTC products found melatonin content ranging from −83% to +478% of the labeled amount; serotonin was detected in 26% of products tested. A pharmacy operating under USP General Chapter <795> compounds melatonin from documented active pharmaceutical ingredient lots with certificate-of-analysis verification, gravimetric weighing, and per-batch identity and strength testing; these controls are not required of the OTC dietary supplement supply chain [usp_795]. The contemporary rise in unsupervised pediatric melatonin ingestions documented in the CDC MMWR analysis [lelak2022] further argues for pharmacy-dispensed and pharmacist-counseled use when the patient is a child or other vulnerable population [burgess2010; herxheimer2002].

Compounded melatonin is dispensed only on a patient-specific prescription and does not substitute for clinician evaluation of the underlying sleep complaint [usp_795]. For primary insomnia in adults under 55, the modest meta-analytic effect on sleep onset latency [brzezinski2005, buscemi2005, auld2017] should be weighed against cognitive behavioral therapy for insomnia as a first-line non-pharmacologic option. For chronobiotic indications (DSWPD, jet lag, shift work), timing, not dose, is the dominant pharmacologic lever [auger2015; liira2014]. RonanRx compounds melatonin only where the prescriber has documented one of the four patient-specific categories above; the brief does not support compounded melatonin as a routine substitute for the OTC supply [lewy1997].

Compounded Melatonin Formulations and Routes

Form	Concentration	Description
Compounded immediate-release oral capsule	Custom, typically 0.1, 0.3, 0.5, 1, 2, 3, or 5 mg per capsule	Documented active ingredient sourcing, gravimetric weighing, and per-batch identity and strength verification under USP <795>. Useful for chronobiotic indications at low doses (0.1, 0.5 mg) and as a reference for adult hypnotic use at higher doses.
Compounded sublingual fast-dissolve tablet or troche	Custom, typically 0.3 to 3 mg	Sublingual absorption avoids first-pass hepatic CYP1A2 metabolism, producing earlier and more reproducible plasma peaks than oral immediate-release at the same dose. Useful when rapid onset before bedtime is clinically desired.
Compounded prolonged-release oral capsule	Typically 1, 2, or 5 mg sustained-release	Designed to approximate the published prolonged-release profile of the EMA-approved Circadin (2 mg) and Slenyto pediatric prolonged-release products. The compounded preparation is not bioequivalent to those products; PK characteristics should not be assumed without local stability and PK data.
OTC dietary supplement (reference product, not RonanRx)	Commonly 1, 3, 5, or 10 mg per tablet, capsule, gummy, or liquid	Sold in the United States under DSHEA. Independent assay of 31 OTC products documented melatonin content from −83% to +478% of label claim and serotonin contamination in a subset [erland2017]. Listed for reference only; RonanRx does not dispense OTC supplements.

Routes used in published literature: oral, sublingual, troche.

Compounded Melatonin Dosing

Route	Population	Range	Duration	Study type
Oral immediate-release	Adults, primary insomnia (sleep onset latency)	0.3, 5 mg taken 30, 60 minutes before desired bedtime	Short-term; effect is modest (approximately 7, 12 minute reduction in sleep onset latency pooled across meta-analyses)	Meta-analyses of randomized trials
	Adults, jet lag			

Route	Population	Range	Duration	Study type
Oral immediate-release		0.5, 5 mg at the destination local bedtime for the first several days after eastward travel across five or more time zones	Until adapted to the destination time zone (typically 3, 5 days)	Cochrane review of randomized trials
Oral immediate-release	Adults, delayed sleep-wake phase disorder	0.3, 0.5 mg approximately 1 hour before the desired (earlier) bedtime, with concurrent behavioral sleep-wake scheduling; timing relative to dim-light melatonin onset is the primary lever	Per individualized treatment plan; sustained effect requires continued behavioral scheduling	AASM clinical practice guideline; randomized clinical trial
Oral immediate-release	Adults, shift-work-related sleep disturbance	1, 5 mg at intended daytime bedtime after a night shift	Per shift schedule	Cochrane review
Oral prolonged-release	Adults aged 55 and older, short-term primary insomnia (EU-approved use)	2 mg taken 1, 2 hours before bedtime	Up to 13 weeks per the EMA Circadin label	EMA-approved labeled regimen; supporting randomized trials
Oral prolonged-release	Children aged 2, 17.5 years with autism spectrum disorder and insomnia (EU-approved use)	2 mg titrated up to 5 mg taken 30, 60 minutes before bedtime	Per individualized treatment plan; phase 3 trial duration was 13 weeks	EMA-approved labeled regimen; supporting phase 3 trial
Oral	Adults, migraine prophylaxis (off-label)	3 mg taken 30 minutes before bedtime	3 months in the Gonçalves randomized trial	Single randomized non-inferiority trial vs amitriptyline 25 mg

Doctor-prescribed and titrated. For circadian indications (delayed sleep-wake phase disorder, jet lag, shift work) the timing of administration relative to the patient's biological night is the dominant pharmacologic lever; doses of 0.3, 0.5 mg given several hours before the endogenous DLMO produce phase advances of approximately 1, 1.5 hours per day [burgess2010, lewy1997, auger2015]. Higher doses do not consistently produce larger phase shifts and risk daytime carry-over. For primary insomnia, doses of 0.3, 5 mg taken 30,

60 minutes before bedtime are typical; the meta-analytic effect on sleep onset latency is modest (approximately 7, 12 minutes) [brzezinski2005, buscemi2005, auld2017].

For pediatric ASD-related insomnia the Gringras phase 3 protocol [gringras2017] used pediatric prolonged-release 2 mg titrated up to 5 mg in children aged 2, 17.5 years. Compounded prolonged-release preparations intended to approximate this profile should be specified by strength and release profile, and the prescriber should be advised that the compounded preparation is not bioequivalent to the EMA-approved pediatric prolonged-release product. For adults aged 55 and older with primary insomnia, the EMA-approved Circadin 2 mg prolonged-release [ema_circadin, lemoine2012] is the published reference; compounded equivalents should be specified analogously.

Most adverse events are mild and dose-related (next-day sleepiness, headache, dizziness); attenuation of dose or earlier timing relative to bedtime is the first tolerability lever. The fluvoxamine-melatonin interaction [hartter2000] substantially raises oral melatonin exposure and the lowest effective dose should be used in patients on potent CYP1A2 inhibitors.

Compounded Melatonin Safety

Short-term safety of oral melatonin at typical clinical doses (0.3, 5 mg in adults, 1, 10 mg in studied pediatric populations) is generally favorable [41]. The Andersen 2016 review [31] and the Besag 2019 systematic review of adverse events [32] in primary and secondary sleep disorders identified the most common adverse events as headache, daytime sleepiness, dizziness, nausea, and hypothermia, all generally mild and self-limited. Serious adverse events directly attributable to melatonin are uncommon in randomized trials at these doses. The Gringras pediatric phase 3 trial [13] reported a similar mild adverse-event profile in children with autism spectrum disorder over 13 weeks.

Longer-term safety data in adults are reassuring but limited [41]. The Wade 6-month trial of prolonged-release melatonin 2 mg in adults aged 55 and older [22] showed no significant difference from placebo in withdrawal effects or rebound insomnia on discontinuation, and no significant change in endogenous melatonin profile or hormonal indices. Long-term pediatric safety beyond approximately 2 years is not well characterized; theoretical concerns about effects on reproductive maturation have not been substantiated in available controlled data but should inform clinician discussion of long-term continuation in children.

Two distinct US-specific safety concerns are relevant to compounded vs OTC supply. First, OTC melatonin content variability documented by Erland and Saxena [33] (−83% to +478% of label across 31 products; serotonin contamination in 26%) is a quality risk specific to the dietary supplement supply. Second, unsupervised pediatric ingestions have risen sharply: the CDC MMWR analysis [34] reported a five-fold increase in pediatric melatonin ingestions reported to US Poison Control between 2012 and 2021, with a notable pandemic-era acceleration; the great majority were asymptomatic but a small fraction required medical attention. Compounded preparations dispensed under USP <795> with documented identity and

strength and with appropriate child-resistant packaging address the first concern; pharmacist counseling on storage and dose limits addresses the second [41].

Contraindications

Known hypersensitivity to melatonin or to excipients in the dispensed preparation is a contraindication. Caution is recommended in autoimmune disease on the basis of preclinical immunomodulatory data, although clinical evidence of harm in autoimmune populations is limited.

Use during pregnancy is generally avoided outside specific research protocols because of limited controlled human data. Use during lactation is similarly limited by data and is generally avoided for routine sleep indications. Patients with documented severe hepatic impairment may have markedly reduced melatonin clearance and require dose reduction or avoidance [31][32].

Drug interactions

Melatonin is primarily metabolized by hepatic CYP1A2 to 6-hydroxymelatonin, with minor contributions from CYP2C19 and CYP1A1. Potent CYP1A2 inhibitors substantially increase oral melatonin exposure. The Härtter 2000 interaction study [28] demonstrated that fluvoxamine coadministration increased the AUC of oral melatonin approximately 17-fold; ciprofloxacin and other CYP1A2 inhibitors produce smaller but clinically meaningful increases. Smoking induces CYP1A2 and reduces oral melatonin exposure [29].

Additive sedation is expected with benzodiazepines, Z-drugs, sedating antihistamines, alcohol, and other CNS depressants. Coadministration with warfarin has been associated with isolated case reports of altered INR; routine INR monitoring is reasonable when melatonin is initiated in a patient on warfarin [29][30][31]. Coadministration with antihypertensives has been associated with both blood-pressure-lowering and -raising signals across small studies; clinically meaningful interaction is not established but should inform monitoring.

Adverse events

Across randomized trials and safety reviews, the most frequently reported adverse events were headache, daytime sleepiness (carry-over sedation), dizziness, nausea, irritability, and vivid dreams. Frequencies are typically in the low single-digit percent above placebo in trials of immediate-release melatonin at doses of 1, 5 mg in adults and 2, 10 mg in pediatric populations [22]. Most events are mild and self-limited, attenuating with dose reduction or earlier timing of administration relative to desired sleep onset [21].

Serious adverse events directly attributable to melatonin are uncommon [32]. Rare reports include seizure recurrence in children with pre-existing epilepsy (causality not established) and isolated reports of altered INR with concurrent warfarin. The CDC MMWR analysis of pediatric melatonin ingestions [34] documented that most unsupervised ingestions were asymptomatic but a small fraction required hospitalization; very-high-dose acute ingestions in children have been associated with central nervous system depression and

gastrointestinal symptoms [3113]. Compounded preparations dispensed with child-resistant packaging and pharmacist counseling address this concern in pediatric households.

Monitoring Compounded Melatonin Therapy

Baseline assessment for sleep complaints should characterize the sleep complaint (sleep onset latency, total sleep time, daytime function, schedule), screen for circadian rhythm sleep-wake disorder, identify contributing medications and substances (caffeine, alcohol, evening light exposure, shift work), and assess for primary sleep disorders requiring separate evaluation (obstructive sleep apnea, restless legs syndrome) [auger2015]. Baseline pregnancy status should be confirmed in patients of reproductive potential.

On therapy, response is assessed by sleep diary or actigraphy over 2, 4 weeks. For chronobiotic indications timing is reviewed in addition to dose. Patients are advised that the effect on sleep onset latency in primary insomnia is modest [brzezinski2005, buscemi2005, auld2017] and that cognitive behavioral therapy for insomnia (CBT-I) remains a first-line option in adults with chronic primary insomnia [auger2015].

Compounded Melatonin in Special Populations

Compounded Melatonin Evidence Quality

Evidence is strongest for circadian rhythm sleep-wake disorders [usp_795]. The AASM 2015 clinical practice guideline [auger2015] issued conditional recommendations for timed strategic melatonin in delayed sleep-wake phase disorder, non-24-hour sleep-wake rhythm disorder, and (with caveats) other intrinsic circadian disorders. The double-blind randomized trial of low-dose melatonin combined with behavioral sleep-wake scheduling in DSWPD [sletten2018], the human phase response curve work [burgess2010, lewy1997], and the Cochrane reviews of jet lag [herxheimer2002] and shift work [liira2014] together provide a coherent and reproducible chronobiotic evidence base. For pediatric autism spectrum disorder, the Gringras phase 3 trial of pediatric prolonged-release melatonin [gringras2017] supported the EMA Slenyto approval, with consistent earlier evidence in pediatric ASD [malow2012, goldman2014, lalanne2021].

Evidence for primary adult insomnia is more modest [wade2010; wade2011]. Three independent meta-analyses [brzezinski2005, buscemi2005, auld2017] converge on a small reduction in sleep onset latency (approximately 7, 12 minutes pooled) and limited effect on total sleep time. The EMA-approved prolonged-release Circadin in adults aged 55 and older is supported by adequately powered trials but is not approved in the United States [usp_795] [ema_circadin; lemoine2012]. Migraine prophylaxis is supported by a single well-conducted non-inferiority RCT vs amitriptyline [goncalves2016] and remains emerging. Oncology adjunct use [mills2005, seely2012] is investigational with concentration of evidence in a single research

group. Antioxidant and general wellness uses [pandi2013, hardeland2012] are supported only by mechanistic and preclinical work.

Two sets of practice-relevant findings frame the 503A rationale [usp_795]. First, the Erland and Saxena 2017 J Clin Sleep Med assay [erland2017] documents that OTC melatonin product content can vary from −83% to +478% of label and that serotonin contamination has been identified in a subset, raising a quality concern specific to the US OTC supply [wade2007]. Second, the CDC MMWR analysis [lelak2022] documents a five-fold rise in unsupervised pediatric ingestions across 2012, 2021. Compounded melatonin under USP <795> with documented identity, strength, and child-resistant dispensing addresses both concerns for the subset of patients where the OTC supply is not clinically appropriate.

Major Compounded Melatonin Clinical Studies

Study	Design	Participants	Duration	Finding
Auger et al. (2015, J Clin Sleep Med), AASM clinical practice guideline	American Academy of Sleep Medicine systematic review and clinical practice guideline for intrinsic circadian rhythm sleep-wake disorders	—	—	Conditional recommendations for timed strategic melatonin in delayed sleep-wake phase disorder and non-24-hour sleep-wake rhythm disorder; emphasis on individualized timing relative to dim-light melatonin onset [auger2015]
Sletten et al. (2018, PLoS Medicine), DSWPD RCT	Double-blind randomized placebo-controlled trial of low-dose melatonin combined with behavioural sleep-wake scheduling for delayed sleep-wake phase disorder in adults	116	4 weeks	Combined low-dose melatonin (0.5 mg) plus behavioural sleep-wake scheduling produced significant advances in sleep timing and improvements in daytime function relative to placebo [sletten2018]
Burgess et al. (2010, J Clin Endocrinol Metab), Human phase response curve	Within-subject phase response curve study of three days of daily melatonin at 0.5 mg vs 3.0 mg vs placebo in healthy adults	—	—	Both doses produced comparable phase advances of approximately 1, 1.5 hours per day when given in the late biological afternoon; 0.5 mg was indistinguishable from 3.0 mg, supporting low-dose dosing for chronobiotic indications [burgess2010]

Study	Design	Participants	Duration	Finding
Lewy et al. (1997, J Biol Rhythms), Phase shifting in sighted humans	Brief review and critique synthesizing earlier work on exogenous melatonin's phase-shifting effects on the endogenous melatonin profile in sighted humans	—	—	Established the human phase response curve concept and the use of dim-light melatonin onset as the timing reference for therapeutic phase shifts [lewy1997]
Herxheimer and Petrie (2002, Cochrane Database Syst Rev), Jet lag	Cochrane systematic review and meta-analysis of randomized trials of melatonin for the prevention and treatment of jet lag	10 trials	—	Substantial reduction in jet-lag symptom severity after eastward travel across five or more time zones; doses of 0.5, 5 mg at destination bedtime were effective; higher doses were not consistently better than 0.5 mg [herxheimer2002]
Liira et al. (2014, Cochrane Database Syst Rev), Shift work	Cochrane systematic review of pharmacological interventions including melatonin for sleepiness and sleep disturbances caused by shift work	—	—	Melatonin taken at intended daytime bedtime after a night shift increased daytime sleep duration by approximately 24 minutes versus placebo, without significant improvement in subjective sleep quality or wakefulness during night shifts [liira2014]
Gringras et al. (2017, J Am Acad Child Adolesc Psychiatry), Pediatric prolonged-release ASD trial	Randomized double-blind placebo-controlled phase 3 trial of pediatric prolonged-release melatonin 2 mg titrated to 5 mg in children aged 2, 17.5 years with autism spectrum disorder and chronic insomnia	125	13 weeks	Sleep latency, total sleep time, and longest sleep episode improved significantly with melatonin versus placebo with acceptable tolerability; basis for the EMA Slenyto approval [gringras2017]
Malow et al. (2012, J Autism Dev Disord), Pediatric ASD dose-finding	Controlled trial examining 1, 3, and 6 mg supplemental melatonin doses in children with autism spectrum disorder	—	—	Sleep onset latency and parent-reported sleep parameters improved across all three doses with comparable tolerability; informed subsequent prolonged-release dosing strategy [malow2012]

Study	Design	Participants	Duration	Finding
Goldman et al. (2014, J Autism Dev Disord), Endogenous and PK profiles in pediatric ASD	Characterization of endogenous and pharmacokinetic melatonin profiles in relation to sleep in children with autism spectrum disorder	—	—	Demonstrated heterogeneous baseline endogenous melatonin profiles and supported pharmacokinetic basis for individualized dosing in pediatric ASD [goldman2014]
Wade et al. (2007, Curr Med Res Opin), Circadin in adults aged 55, 80	Randomized double-blind placebo-controlled trial of prolonged-release melatonin 2 mg in adults aged 55, 80 with primary insomnia	—	3 weeks	Improved sleep quality and morning alertness without rebound on discontinuation; informed the EMA Circadin approval [wade2007]
Wade et al. (2010, BMC Medicine), 6-month Circadin trial	Randomized placebo-controlled trial of prolonged-release melatonin 2 mg in primary insomnia for 6 months, examining age and baseline endogenous melatonin as moderators	—	6 months	Sustained efficacy in adults aged 55 and older with no significant rebound or withdrawal effects; basis for the long-term safety position of Circadin [wade2010]
Wade et al. (2011, Curr Med Res Opin), Age cut-off analysis	Pooled analysis of prolonged-release melatonin 2 mg trials examining the age cut-off for short- and long-term efficacy	—	—	Supported the 55-year age threshold for the EMA Circadin indication [wade2011]
Lemoine and Zisapel (2012, Expert Opin Pharmacother), Circadin review	Comprehensive review of prolonged-release melatonin (Circadin) for the treatment of insomnia	—	—	Synthesized pharmacology, efficacy, and tolerability evidence supporting the EMA approval; positioned prolonged-release as the dosage form most aligned with the duration of endogenous melatonin [lemoine2012]
Brzezinski et al. (2005, Sleep Med	Meta-analysis of 17 randomized trials of exogenous melatonin on sleep parameters in	—	—	Reduced sleep onset latency by approximately 4 minutes, increased sleep efficiency by approximately 2%, and

Study	Design	Participants	Duration	Finding
Rev), Meta-analysis on sleep	healthy and insomniac adults			increased total sleep time by approximately 13 minutes, modest but reproducible effects [brzezinski2005]
Buscemi et al. (2005, J Gen Intern Med), Primary sleep disorders meta	AHRQ-supported meta-analysis of randomized trials of exogenous melatonin for primary sleep disorders	—	—	Reduced sleep onset latency by approximately 7.2 minutes (95% CI 2.9, 11.4) without significant effect on sleep efficiency or total sleep time [buscemi2005]
Buscemi et al. (2006, BMJ), Secondary sleep disorders meta	Meta-analysis of randomized trials of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction	—	—	No statistically significant effect on sleep onset latency, sleep efficiency, or total sleep time in secondary sleep disorders; supported the distinction between circadian and primary insomnia indications [buscemi2006]
Auld et al. (2017, Sleep Med Rev), Adult primary sleep disorders review	Systematic review of randomized trials of melatonin for primary adult sleep disorders	—	—	Confirmed the small but reproducible meta-analytic effect on sleep onset latency, with the strongest signal in delayed sleep-wake phase disorder and modest effect in primary insomnia [auld2017]
Gonçalves et al. (2016, J Neurol Neurosurg Psychiatry), Migraine prophylaxis RCT	Randomized double-blind placebo-controlled trial of melatonin 3 mg vs amitriptyline 25 mg vs placebo for migraine prevention	196	3 months	Melatonin and amitriptyline both reduced headache frequency more than placebo; melatonin was non-inferior to amitriptyline with significantly fewer adverse events (weight loss vs weight gain; lower anticholinergic burden) [goncalves2016]
Mills et al. (2005, J Pineal Res), Oncology adjunct meta-analysis	Systematic review and meta-analysis of 10 randomized controlled trials of melatonin as	—	—	Reductions in one-year mortality (RR 0.66; 95% CI 0.59, 0.73) and treatment-related toxicity; preliminary signal limited by methodologic

Study	Design	Participants	Duration	Finding
	adjunct treatment for solid tumor cancers			concerns and concentration of trials in a single research group [mills2005]
Seely et al. (2012, Integr Cancer Ther), Updated oncology adjunct meta	Systematic review and meta-analysis of randomized trials of melatonin as adjuvant cancer care with and without chemotherapy	—	—	Reported similar directional benefit on one-year mortality and treatment-related toxicity; limitations of the underlying evidence base persisted [seely2012]
Härtter et al. (2000, Clin Pharmacol Ther), Fluvoxamine interaction	Pharmacokinetic crossover study of oral melatonin with and without fluvoxamine coadministration in healthy adults	—	—	Fluvoxamine increased the AUC of oral melatonin approximately 17-fold, identifying CYP1A2 as the principal metabolizing pathway and establishing a clinically important drug-drug interaction [hartter2000]
Harpsøe et al. (2015, Eur J Clin Pharmacol), Pharmacokinetics review	Systematic review of the clinical pharmacokinetics of exogenous melatonin	—	—	Oral bioavailability is low and variable (3, 15%); time to maximum concentration is 20, 90 minutes for immediate-release; half-life is 20, 60 minutes; CYP1A2 is the principal metabolizing enzyme [harpsoe2015]
Andersen et al. (2016, Clin Drug Investig), Repeated-dose pharmacokinetics	Pharmacokinetics of repeated melatonin drug administrations prior to and after surgery in adults	—	—	Repeated oral and intravenous melatonin showed no accumulation; reproducible plasma profiles supported predictable clinical dosing [andersen2016_pk]
Andersen et al. (2016, Clin Drug Investig), Safety review	Systematic review of the safety of melatonin in humans across short-term clinical trials	—	—	Confirmed favorable short-term safety with mild headache, daytime sleepiness, dizziness, and nausea as the most common adverse events; serious adverse events were uncommon [andersen2016_safety]

Study	Design	Participants	Duration	Finding
Besag et al. (2019, CNS Drugs), Adverse events systematic review	Systematic review of adverse events associated with melatonin for primary or secondary sleep disorders	—	—	Reaffirmed mild adverse-event profile across the trial corpus; identified data gaps for very long-term and very young pediatric use [besag2019]
Erland and Saxena (2017, J Clin Sleep Med), OTC content variability	Quantitative assay of melatonin content in 31 commercially available natural-health-product melatonin formulations purchased in Canada	—	—	Melatonin content ranged from −83% to +478% of label; serotonin was identified as a contaminant in 26% of products; underscored the absence of standardized quality control across the OTC supplement supply [erland2017]
Lelak et al. (2022, MMWR), Pediatric ingestions	Retrospective analysis of US Poison Control reports of pediatric melatonin ingestions, 2012, 2021	—	—	Pediatric ingestions rose approximately five-fold over the decade with marked pandemic-era acceleration; most were asymptomatic but a small fraction required medical attention; supported messaging on storage and child-resistant packaging [lelak2022]
Aulinas (2019, Endotext), Pineal physiology	Comprehensive review of pineal gland physiology and melatonin	—	—	Consolidates pineal anatomy, melatonin biosynthesis, suprachiasmatic-nucleus regulation, and clinical implications of melatonin physiology [aulinas2019]
Dubocovich (2007, Sleep Medicine), Receptor review	Review of melatonin receptor pharmacology (MT1 and MT2) and their role in sleep and circadian rhythm regulation	—	—	Synthesized the receptor pharmacology distinguishing chronobiotic (MT2-mediated) from acute hypnotic (MT1-mediated) actions of melatonin [dubocovich2007]
	Molecular cloning and expression of the high-affinity Mel1a (MT1)	—	—	Established the molecular identity of the MT1 receptor and supported functional

Study	Design	Participants	Duration	Finding
Reppert et al. (1995, Neuron), Mel1a (MT1) cloning	melatonin receptor from chick brain			studies of its role in the SCN [reppert1995_mt1]
Reppert et al. (1995, PNAS), Mel1b (MT2) cloning	Molecular characterization of a second melatonin receptor (Mel1b, MT2) expressed in human retina and brain	—	—	Identified MT2 as a distinct high-affinity melatonin receptor with retinal expression; established the receptor basis for tissue-specific melatonin actions [reppert1995_mt2]
Liu et al. (1997, Neuron), SCN dissection	Electrophysiological dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock in rat	—	—	Demonstrated that melatonin acutely suppresses SCN neuronal firing and produces a phase shift through a distinct mechanism, substrate for the dual chronobiotic-plus-hypnotic clinical profile [liu1997]
Lalanne et al. (2021, Int J Mol Sci), ASD pharmacokinetics and clinical use	Review of melatonin pharmacokinetics and clinical use in autism spectrum disorder	—	—	Consolidated pediatric ASD evidence base and pharmacokinetic considerations supporting prolonged-release dosing in this population [lalanne2021]

Compounded Melatonin Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Melatonin is a small lipophilic indoleamine (MW 232). After oral immediate-release administration, time to maximum plasma concentration is approximately 20, 90 minutes; oral bioavailability is low and highly variable (literature ranges from 3% to 15%) because of substantial first-pass hepatic metabolism. Terminal half-life is approximately 20, 60 minutes for immediate-release oral and intravenous routes [harpsoe2015, andersen2016_pk]. Plasma protein binding is approximately 50, 60% (predominantly albumin). The molecule crosses the blood-brain barrier and the placenta.

Metabolism is primarily hepatic via CYP1A2 to 6-hydroxymelatonin, which is then sulfated and excreted in urine. Minor pathways involve CYP2C19 and CYP1A1. Potent CYP1A2 inhibitors (notably fluvoxamine) markedly increase oral exposure: the Härtter 2000 interaction study [hartter2000] reported an

approximately 17-fold increase in AUC with fluvoxamine coadministration. Smoking is a CYP1A2 inducer and reduces oral exposure.

Prolonged-release oral preparations (the EMA-approved Circadin 2 mg [ema_circadin, lemoine2012] and the pediatric Slenyto product [ema_slenyto, gringras2017, lalanne2021]) are formulated to extend plasma melatonin above threshold across a larger fraction of the night than immediate-release at the same nominal dose. Sublingual administration avoids first-pass metabolism and produces faster and more reproducible plasma peaks. Compounded prolonged-release or sublingual preparations should not be assumed bioequivalent to the EMA-approved reference products without local stability and PK data.

Pharmacodynamics

Pharmacodynamic effects partition into a chronobiotic action (timed phase shift of the central circadian pacemaker via MT2 receptors in the SCN) and a milder hypnotic action (acute suppression of SCN firing via MT1, plus reduction of core body temperature). The chronobiotic action is the dominant therapeutic mechanism for delayed sleep-wake phase disorder, jet lag, and shift-work-related sleep disturbance; the hypnotic action contributes to the small effect on sleep onset latency in primary insomnia [auger2015; brzezinski2005].

The relevant clinical pharmacodynamic endpoints are sleep onset latency, total sleep time, sleep efficiency, dim-light melatonin onset (DLMO), the most widely used marker of internal circadian phase, and, for pediatric ASD, parent-reported sleep parameters validated against actigraphy [gringras2017] [burgess2010; lewy1997].

↓↑ Comparing Compounded Melatonin Formulations

Immediate-release oral melatonin produces a rapid plasma peak appropriate for sleep-onset and chronobiotic dosing where timing relative to DLMO is the principal lever [burgess2010, harpsoe2015]. Sublingual fast-dissolve administration bypasses first-pass metabolism and may produce faster onset and more reproducible peaks than oral immediate-release at the same dose, useful when rapid onset is clinically desired.

Prolonged-release oral melatonin (the EMA-approved Circadin 2 mg and pediatric Slenyto products) is designed to maintain plasma melatonin above threshold across a larger fraction of the night, approximating the endogenous overnight profile rather than producing an early-night plasma spike [ema_circadin; ema_slenyto; lemoine2012]. Compounded prolonged-release preparations are not bioequivalent to the EMA-approved reference products and require separate stability and PK considerations.

OTC dietary supplement melatonin is a distinct supply chain not subject to drug-product quality requirements; independent assay of OTC products [erland2017] has documented marked deviation from label content. Compounded 503A melatonin is dispensed only on a patient-specific prescription with documented identity, strength, and excipient profile under USP <795> [usp_795]; it is not a generic

equivalent to OTC supplements and is not a substitute for OTC use where the OTC supply is clinically appropriate [gringras2017].

Compounded Melatonin Storage and Handling

Compounded oral and sublingual melatonin preparations are stored at controlled room temperature (20, 25°C) protected from light, with beyond-use date assignment per USP <795> stability data [usp_795]. Cold-chain shipping is not required for solid oral or sublingual dosage forms.

Patients are advised to store the dispensed product out of reach of children given the documented rise in unsupervised pediatric melatonin ingestions in the United States [lelak2022] [usp_795]. Child-resistant packaging is used for pediatric and household-shared preparations.

Compounded Melatonin Compounding & Operations

503A compounding

Compounded melatonin is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares nonsterile oral and sublingual preparations per USP General Chapter <795>, the official compendial standard for nonsterile pharmaceutical compounding, with documented active pharmaceutical ingredient sourcing, certificate-of-analysis verification, gravimetric weighing, and per-batch identity and strength verification [usp_795]. Beyond-use dating, ingredient identity verification, and stability assessment follow USP <795> requirements.

503A compounding of melatonin is appropriate when one of the patient-specific clinical-need categories is documented: custom strength outside commercially marketed increments (notably 0.1, 0.5 mg for chronobiotic indications), dosage form not commercially available (custom-strength sublingual fast-dissolve, compounded prolonged-release), excipient or allergen sensitivity to OTC formulations, or pediatric dose individualization where the OTC supply is not standardized [fda503a; gringras2017]. The published evidence on OTC content variability [erland2017] and pediatric ingestion patterns [lelak2022] supports the 503A rationale for these specific populations but does not support compounded melatonin as a routine substitute for the OTC supply [burgess2010].

Pharmacist review

Each prescription for compounded melatonin undergoes pharmacist review prior to dispensing [brzezinski2005; buscemi2005; auld2017]. The review confirms: a documented patient-specific clinical reason that the OTC dietary supplement supply is not appropriate (custom strength, dosage form not commercially available, excipient or allergen sensitivity, pediatric dose individualization); a prescribed regimen consistent with the published evidence base for the indication; absence of contraindications; and

concomitant medication review with attention to potent CYP1A2 inhibitors (notably fluvoxamine) [hartter2000] and other interacting agents [liira2014; gringras2017].

For pediatric dispensing the pharmacist confirms appropriate child-resistant packaging and counsels caregivers on safe storage given the documented rise in unsupervised pediatric ingestions [lelak2022]. For chronobiotic indications the pharmacist confirms that the prescribed timing matches the indication (early-evening dose for phase advance; bedtime dose at destination for jet lag) and counsels the patient on the importance of consistent timing relative to dim-light melatonin onset where applicable [burgess2010, auger2015] [herxheimer2002].

Quality and traceability

Active pharmaceutical ingredient is sourced from FDA-registered facilities with documented certificates of analysis. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, identity and strength test results, and dispensing pharmacist of record [usp_795]. Finished product lot records are retained per state board of pharmacy retention requirements. This per-batch documentation is the principal quality differentiator from the OTC dietary supplement supply, where independent assay has documented wide deviation from label content [erland2017].

Cold chain

Compounded solid oral and sublingual melatonin preparations are stable at controlled room temperature and do not require cold-chain shipping [usp_795]. Patients are advised to store dispensed product at controlled room temperature protected from light, and out of reach of children given documented pediatric ingestion patterns [lelak2022].

Frequently Asked Questions About Compounded Melatonin

Is compounded melatonin the same as the melatonin sold in stores?

No. Over-the-counter melatonin in the United States is regulated as a dietary supplement under DSHEA [fda_dshea; usp_795]. Independent assay of OTC melatonin products has documented melatonin content ranging from approximately −83% to +478% of label, with serotonin contamination in a subset [erland2017]. A compounded preparation is dispensed by a pharmacy on a patient-specific prescription with documented identity, strength, and excipient profile under USP <795>.

Is there an FDA-approved melatonin product in the United States?

No. There is no FDA-approved melatonin drug product in the United States [fda_dshea]. In the European Union, prolonged-release melatonin 2 mg (Circadin) is EMA-approved for short-term primary insomnia in adults aged 55 and older, and pediatric prolonged-release melatonin (Slenyto) is EMA-approved for insomnia in children with autism spectrum disorder [ema_circadin; ema_slenyto].

When is compounded melatonin appropriate?

When the prescribing clinician documents a patient-specific reason that the OTC supply cannot meet, for example, a custom low dose of 0.1, 0.5 mg for circadian phase advance, a sublingual fast-dissolve at a custom strength, an excipient or allergen sensitivity to OTC formulations, or pediatric dose individualization where OTC pediatric content variability is a documented concern [erland2017; burgess2010; gringras2017].

What dose should I take for jet lag?

Per the Cochrane review of melatonin for jet lag, doses of 0.5, 5 mg taken at the destination local bedtime for the first several days after eastward travel across five or more time zones reduce jet lag symptoms [herxheimer2002]. Higher doses are not consistently more effective than 0.5 mg. Specific dosing should be discussed with a clinician.

Does melatonin help with regular adult insomnia?

Meta-analyses of randomized trials show only a small effect on the time it takes to fall asleep, roughly 7 to 12 minutes pooled across studies, and limited effect on total sleep time [brzezinski2005; buscemi2005; auld2017]. For chronic insomnia in adults under 55, cognitive behavioral therapy for insomnia (CBT-I) is generally a first-line option.

Is melatonin safe in children?

Short-term randomized trials in children with autism spectrum disorder have shown an acceptable safety profile over up to 13 weeks [gringras2017]. Longer-term pediatric safety is less well characterized. Unsupervised pediatric ingestions in the United States have risen sharply between 2012 and 2021, so child-resistant packaging and safe storage are important [lelak2022].

Are there important drug interactions?

Yes. Potent CYP1A2 inhibitors substantially raise oral melatonin exposure, fluvoxamine increased the area under the curve approximately 17-fold in a controlled study [hartter2000; andersen2016_safety]. Additive sedation is expected with benzodiazepines, Z-drugs, sedating antihistamines, and alcohol. INR may shift with warfarin in isolated reports.

Does RonanRx sell compounded melatonin directly to patients?

No. Compounded melatonin requires a patient-specific prescription written by a licensed clinician for an identified patient with a documented clinical reason that the OTC supply is not appropriate, plus pharmacist review before dispensing. RonanRx is not a direct-to-consumer storefront and is not a substitute for OTC use where OTC is clinically appropriate [fda503a].

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How to Access Compounded Melatonin

Compounded Compounded Melatonin is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Compounded Melatonin, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)