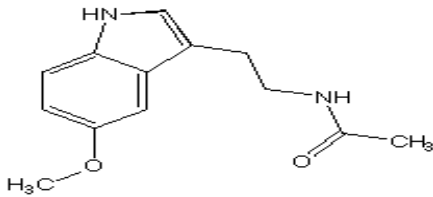


Melatonin



Name of Herb or Supplement: Melatonin

Scientific and common names: N-acetyl-5-methoxytryptamine, Melatonin, Ester-C Nighttime Formula,¹ Melatonin CR.¹

Description of active ingredients: N-acetyl-5-methoxytryptamine is a neurohormone produced by pinealocytes in the pineal gland located right at the center of the brain and responsible for biological, circadian rhythm of our body.¹⁻³ Melatonin was discovered by Lerner et al. in 1958 from bovine pineal glands in search of the amphibian skin-lighting factor.² Later studies have found the presence of melatonin in the pineal gland and the blood during the dark and absence during the light period leading to the conviction that melatonin is a chemical messenger of diurnal cycles and synchronizer of endogenous rhythms.

MOA: Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced by pinealocytes in the pineal gland during the dark hours (night) of the day-night cycle.¹⁻² Serum levels of melatonin are very low during most of the day, and it has been labeled the "hormone of darkness". Melatonin is involved in the induction of sleep, and may play a role in the internal synchronization of the mammalian circadian system.¹⁻³

Current indications and efficacy:

- For occasional self-treatment of mild insomnia^{1-3,5,10}, possibly effective.¹ In a double-blind, placebo-controlled study, subjects who slept normally (n = 15) or exhibited actigraphically confirmed decreases in sleep efficiency (n = 15) received, in randomized order, a placebo and three melatonin doses (0.1, 0.3, and 3.0 mg) orally 30 min before bedtime for a week. The physiologic melatonin dose (0.3 mg) restored sleep efficiency (P < 0.0001).¹⁰ An oral dose of melatonin 75 milligrams has been used in chronic INSOMNIA.¹

Original Author Folami Osikoya
Reviewed 5/14/03 Susan Paulsen PharmD

- For treatment of jet-lag sleep^{1,4-6}, effective not FDA approved.¹ In a double-blind placebo-controlled trial (Petrie et al, 1993) demonstrated significant less jet lag and sleep disturbance following flight when compared to placebo.⁶ Usual doses of oral melatonin 5 mg daily for 3 days prior to departure (between 10 am and 6 pm local time), then 5 milligrams for 4 additional days (usually between 10 pm and midnight local time), beginning on the day of the flight.⁶
 - Adjunctive treatment of insomnia related to major depression^{1-3,5}, ineffective.¹
 - Improving sleep quality related to rotating-shift work^{1,4-5}, effective but not FDA approved.¹ Melatonin 5 milligrams orally 30 minutes prior to bedtime.¹
 - Treatment of delayed sleep phase syndrome resulting from circadian rhythm disruption, including patients with autism, blindness, Rett's syndrome or developmental disabilities.^{1,3,7} Possibly effective not FDA approved.¹ In a randomized, double blind, placebo-controlled crossover study (Kayomuv L et al 2000), melatonin ameliorate some symptoms of delayed sleep phase syndrome in 20 patients that participated in the trial when compared to placebo.⁷ Melatonin 5 milligrams orally at the usual bedtime has been useful in treating blind patients with desynchronized sleep-wake cycles
 - Treatment of subjective tinnitus¹, possibly effective not FDA approved.¹ Rosenberg et al 1998, a randomized prospective, double blind, placebo-controlled demonstrated the usefulness of melatonin in the treatment of tinnitus when compared to placebo.⁸
 - Cancer^{1,4-5}, effective not FDA approved.¹ Cos S et al 2001, demonstrated that melatonin at concentrations of 1 nM and 10 pM (within the range of concentrations that correspond to physiological night-time and daytime levels in human blood) significantly inhibited proliferation in both melanoma cell lines.⁹ Oral melatonin 40 or 50 milligrams was given once daily at night, initiated 7 days prior to interleukin-2 (induction phase) and continued throughout the cycle.¹
- Contraception^{1,4-5}, possibly effective not FDA approved.¹ Oral melatonin 40 or 50 milligrams was given once daily at night, initiated 7 days prior to interleukin-2 (induction phase) and continued throughout the cycle.¹

Contraindications/allergies: Since rigid quality control standards are not required for melatonin and substantial variability can occur in both the potency and the purity of these

products. Impurities may cause allergic reactions such as **bovine protein hypersensitivity**¹ since some melatonin products are derived from the pineal glands of beef cattle. Melatonin is not recommended in neonates, infants, or children without the approval and observation of a health care professional.¹ Caution is also warranted in the elderly due to limited study of melatonin in this patient population at this time.¹ Melatonin may cause drowsiness. Driving or operating machinery, or performing other tasks that require mental alertness requires caution when taking melatonin.¹ Melatonin should be considered contraindicated in females who are trying to conceive, because has a hormone melatonin modulates steroid hormone actions, including reproductive and mammary tissues.¹ Melatonin has also been shown to inhibit ovulation in higher doses and may affect reproductive capacity, thus may impact infertility.¹ Furthermore, melatonin is contraindicated in pregnancy, because endogenous melatonin crosses the placenta and enters the fetal circulation, thus setting circadian rhythm influence in the utero.¹ Melatonin should be used with caution in patients with renal and hepatic disease, and also patients undergoing treatment for neoplastic or endocrine disease and immunosuppressive patients.¹

Dosage forms:

- 1 mg, 3 mg, 500mcg capsule.¹
- 3 mg extended-release capsule.¹
- 1 mg/ml liquid.¹
- 1 mg, 1.5 mg, 2 mg and 3 mg tablet.¹

Recommended doses, duration:

- Insomnia: Adults 0.3 to 3 mg PO every evening approximately 1 to 2 hours before bedtime. May take up to 6 mg PO at bedtime as needed. Use should not exceed 2 weeks without prescriber consultation.¹
- Improving sleep quality related to rotating-shifts work: Adult 5-10 mg PO taken at 7 AM or 8 AM prior to daytime sleep periods, or taken 2 hours prior to bedtime at night.¹
- Jet-lag sleep: Adults 3 to 6 mg PO taken nightly at 2200 to 2400 hours local time after destination arrival may help adaptation to different time zones.^{1,5} Melatonin may be administered for up to 5 nights as needed.¹ Treatment may not completely eliminate all jet-lag symptoms. More study is needed

- Delayed sleep phase syndrome resulting from circadian rhythm disruption, including patients with autism, blindness, Rett's syndrome, or developmental disabilities: Adults 5 to 10 mg PO once daily at bedtime has been used in the blind to entrain circadian rhythms to a 24 hour day and improve sleep patterns.¹ Once entrained, doses should be reduced to over a 3 months period to a maintenance dosage of 0.5 mg PO per day.¹
- Subjective tinnitus: Adults 3 mg PO at bedtime has been used.¹
- Insomnia related to depression: Adults 5 to 10 mg PO taken 1 to 2 hours prior to bed.^{1,5}
- Cancer: Adults 40 to 50 mg tablet PO once daily at night, initiate 7 days prior to interleukin-2 and continued throughout the cycle.^{1,5}

Drug interactions and Drug-Disease interactions: In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites; this may result in clinically significant drug interactions.¹ Fluvoxamine induced an increase in the AUC and peak concentrations of melatonin 23-fold and 12-fold, respectively after co-administration of 5 mg melatonin dose in several healthy volunteers.¹ The interaction may increase the sedative effects of melatonin.¹ The antibacterial effects of isoniazid may be potentiated by melatonin.¹ However, it is unknown what effect melatonin has on isoniazid, INH activity, serum concentrations, or tuberculosis infection when the two therapies are combined. Melatonin may impair the efficacy of some calcium-channel blockers, and caution is advised with concurrent use.¹

Other safety issues: Possible drug interaction with the following drugs

- Blood pressure medication such as nifedipine.¹ Increases blood pressure by competing with nifedipine for calcium channels
- Medication for sleep.¹ e.g. diazepam decrease melatonin levels significantly.

For many OTC products sold as nutritional supplements, interactions with other medication are sometimes unknown, so you should always be careful when mixing these remedies with traditional medications. If you take any other medications, always consult with your health care professional before taking melatonin. Report the following side effects to your health

care provided as soon as possible; confusion, forgetfulness, depressed mood, nervousness, rash, rapid heart rate or palpitation. Do not drink alcohol while taking melatonin, and do not take melatonin if you are sensitive to bovine products because some melatonin products are derived animals.

Different brands of melatonin might contain different amount of active ingredients so be careful to use the same brand. It is recommended that you use a brand from a reliable manufacturer and one that has been standardized. A standardized (FDA standard) product is more likely to contain the same amount of hormone from dose to dose. Your health care professional or pharmacist can assist you in finding a standardized product. Keep medicine out of reach of children.

References:

1. Micromedex ® Health Series: MICREMEDEX, Inc., Englewood, Colorado (Edition expires (03/2003)).
2. Cajochen C, Krauchi K, Wirz-Justice A, et al. Role of melatonin in the regulation of human circadian rhythm and sleep. *J Neuroendocrinol* 2003 Apr;15(4):432-7
3. Sack RL, Lewy AJ, et al. Circadian rhythm sleep disorders: lesions from the blind. *Sleep Med Rev* 2001 Jun;5(3):189-206
4. Shawn M. Talbott. *A Guide to Understanding Dietary Supplements*. Haworth Press Inc. New York 2003 pg 324-325
5. Michael T, Murray ND, et al. *Encyclopedia of Nutritional Supplements: The Essential Guide for improving Your Health Naturally*. Prima Health Rocklin, CA. pg 351-355
6. Petrie K, Dawson A, Thompson L, Brook R et al. A Double-Blind Trial of Melatonin as a Treatment for Jet-Lag International Cabin Crew
7. Kayumov L, Brown G, Jindal R, Buttoo K, et al. A Randomized, Double-Blind Placebo-Controlled Crossover Study of the Effect of Exogenous Melatonin on Delayed Sleep Phase Syndrome. *Psychomatic Med* 2001 Jan 63:40-48.
8. Rosenberg et al. Effect of Melatonin on Tinnitus. *Laryngoscope* 1998 Mar;108 (3):305-10
9. Cos S, Garic-Bolado A, et al. Direct antiproliferative effect of melatonin on two metastatic sublines of mouse meatonin. *Melanoma Res* 2001 Apr;11(2):197-201
10. Zhdanova IV, Wurtman RJ, Regan MM, et al. Melatonin treatment for age-related insomnia. *J Clin Endocrinol Metab* 2001 Oct;86(10):4727-30