<u>Melatonin</u>

Melatonin is a hormone secreted by the pineal gland in the brain. It helps regulate other hormones and maintains the body's **circadian rhythm**. The circadian rhythm is an internal 24-hour "clock" that plays a critical role in when we fall asleep and when we wake up. When it is dark, your body produces more melatonin; when it is light, the production of melatonin drops. Being exposed to bright lights in the evening or too little light during the day can disrupt the body's normal melatonin cycles. For example, jet lag, shift work, and poor vision can disrupt melatonin cycles. Melatonin also helps control the timing and release of **female reproductive hormones**. It helps determine when a woman starts to menstruate, the frequency and duration of menstrual cycles, and when a woman stops menstruating (menopause).

Melatonin has **strong antioxidant effects**. Preliminary evidence suggests that it may help **strengthen the immune system**.

Melatonin has been approved by the TGA for use in Australia to treat insomnia.

<u>Uses</u>

Insomnia

Studies suggest that melatonin supplements may help people with disrupted circadian rhythms (such as people with jet lag or those who work the night shift) and those with low melatonin levels to sleep better.

Clinical studies suggest that melatonin is more effective than a placebo in reducing the time it takes to fall asleep, increasing the number of sleeping hours, and boosting daytime alertness. One study of 334 people found that sustained-release melatonin seemed to help people fall asleep faster, sleep better, be more alert in the morning, and improve quality of life in people with primary insomnia.

Menopause

Melatonin supplements may help with sleep problems associated with menopause.

Breast Cancer

Several studies suggest that **low melatonin levels** may be associated with **breast cancer risk**. For example, women with breast cancer tend to have lower levels of melatonin than those without the disease. Laboratory experiments have found that low levels of melatonin stimulate the growth of certain types of breast cancer cells, while adding melatonin to these cells slows their growth.

In another small study of women who were taking tamoxifen for breast cancer but seeing no improvement, adding melatonin caused tumors to modestly shrink in more than 28% of the women.

Prostate Cancer

Studies show that people with prostate cancer have lower melatonin levels than men without the disease. In test tube studies, melatonin blocks the growth of prostate cancer cells. In one small-scale study, melatonin -- combined with conventional medical treatment -- improved survival rates in 9 out of 14 men with metastatic prostate cancer. Interestingly, since meditation may cause melatonin levels to rise it appears to be a valuable addition to the treatment of prostate cancer. More research is needed before doctors can make recommendations in this area.

Attention Deficit Hyperactivity Disorder (ADHD)

Some evidence suggests that melatonin may help promote sleep in children with ADHD, although it does not seem to improve the behavioral symptoms of ADHD.

Irritable Bowel Syndrome

Some preliminary studies suggest that people with IBS who take melatonin reduce some symptoms of IBS, such as abdominal pain.

Available Forms:

Melatonin is available as tablets, capsules, cream, and lozenges that dissolve under the tongue.

Adult

- Insomnia: 1 to 3 mg 1 hour before bedtime is usually effective, although doses as low as 0.1 -0.3 mg may improve sleep for some people. If 3 mg per night does not work, 5 - 6 mg 1 hour before bedtime can be tried. The right dose should produce restful sleep with no daytime irritability or fatigue.
- Jet lag: 0.5 5 mg of melatonin 1 hour prior to bedtime at your final destination has been used in several studies. Another approach that has been used is 1 - 5 mg 1 hour before bedtime for 2 days prior to departure and for 2 - 3 days upon arrival at final destination.

Precautions:

Some people may have vivid dreams or nightmares when they take melatonin.

Melatonin can cause drowsiness if taken during the day. If you are drowsy the morning after taking melatonin, you may require a lower dose.

Uncommon side effects include stomach cramps, dizziness, headache, irritability.

Pregnant or nursing women should not take melatonin.

Possible Interactions:

If you are being treated with any of the following medications, you should not use melatonin without first discussing it with your Australian Menopause Centre health care provider.

Antidepressant medications -- Melatonin may reduce the antidepressant effects of fluoxetine (Prozac).

Benzodiazepines -- The combination of melatonin and some benzodiazepines improved sleep quality in one study. In addition, a few reports have suggested that melatonin supplements may help people stop using long-term benzodiazepine therapy. (Benzodiazepines are habit-forming.)

Blood pressure medications -- Medications in a class called calcium channel blockers may lower melatonin levels. Calcium channel blockers include:

- Amlodipine (Norvasc)
- Verapamil (Isoptin)
- Diltiazem (Cardizem)
- Felodipine (Plendil)

Beta-blockers -- Use of beta-blockers may lower melatonin levels in the body. Betablockers include:

- Atenolol (Tenormin)
- Metoprolol (Lopressor, Toprol XL)
- Propranolol (Inderal)

Blood-thinning medications (anticoagulants) -- Melatonin may increase the risk of bleeding from anticoagulant medications such as warfarin (Coumadin).

Nonsteroidal anti-inflammatory drugs (NSAIDs) -- NSAIDs such as ibuprofen may lower levels of melatonin in the blood.

Steroids and immunosuppressant medications -- Melatonin may cause these medication to lose their effectiveness. Do not take melatonin with corticosteroids or other medications used to suppress the immune system.

Other -- Caffeine, tobacco, and alcohol can all lower levels of melatonin in the body.

References

Acuna-Castroviejo D, Escames G, Rodriguez MI, Lopez LC. Melatonin role in the mitochondrial function. *Front Biosci.* 2007;12:947-63.

Altun A, Ugur-Altun B. Melatonin: therapeutic and clinical utilization. Int J Clin Pract. 2007;61(5):835-45.

Arendt J. Melatonin, circadian rhythms and sleep. New Engl J Med; 2000;343(15):1114-1116. Attele AS, Xie JT, Yuan CS. Treatment of insomnia: an alternative approach. Altern Med Rev. 2000;5(3):249-259.

Barcelo E. Melatonin -- estrogen interactions in breast cancer. J of Pineal Res. 2005;38:217-222.

Barcelo E. melatonin and mammary cancer: a short review. Endocrine-Related Cancer. 2003;10:153-159.

Bazil CW, Short D, Crispin D, Zheng W. Patients with intractable epilepsy have low melatonin, which increases following seizures. *Neurology*. 2000;55(11):1746-1748.

Brown GM, Pandi-Perumal SR, Trakht I, Cardinali DP. Melatonin and its relevance to jet lag. *Travel Med Infect Dis.* 2009 Mar:7(2):69-81 Review

Bylesjo I, Forsgren L, Wetterberg L. Melatonin and epileptic seizures in patients with acute intermittent porphyria. *Epileptic Disord*. 2000;2(4):203-208.

Chang FY, Lu CL. Treatment of irritable bowel syndrome using complementary and alternative medicine. *J Chin Med Assoc.* 2009 Jun;72(6):294-300. Review.

Cornelissen G, Halberg F, Burioka N, Perfetto F, Tarquini R, Bakken EE. Do plasma melatonin concentrations decline with age? *Am J Med.* 2000;109(4):343-345.

Cos S, Sanchez-Barcelo EJ. Melatonin and mamary pathological growth. *Frontiers Neuroendo*. 2000;21:133-170. Cos S, Sanchez-Barcelo EJ. Melatonin, experimental basis for a possible application in breast cancer prevention and treatment. *Histo Histopath*. 2000;15:637-647.

Eck-Enriquez K, Kiefer TL, Spriggs LL, Hill SM. Pathways through which a regimen of melatonin and retinoic acid induces apoptosis in MCF-7 human breast cancer cells. *Breast Cancer Res Treat*. 2000;61(3):229-239.

Gordon N. The therapeutics of melatonin: a paediatric perspective. Brain Dev. 2000;22(4):213-217.

Herxheimer A, Petrie KJ. Melatonin for preventing and treating jet lag. *Cocharane Database Syst Rev.* 2001;(1):CD001520. Jacobson JS, Workman SB, Kronenberg F. Research on complementary/alternative medicine for patients with breast cancer: a review of the biomedical literature. *J Clin Onc.* 2000;18(3):668-683.

Kaneko S, Okumura K, Numaguchi Y, Matsui H, Murase K, Mokuno S, et al. Melatonin scavenges hydroxyl radical and protects isolated rat hearts from ischemic reperfusion injury. *Life Sciences*. 2000;67(2):101-112.

Lagneux C, Joyeux M, Demenge P, Ribuot C, Godin-Ribuot D. Protective effects of melatonin against ischemia-reperfusion injury in the isolated rat heart. *Life Sciences*. 2000;66(6):503-509.

Lewy AJ, Emens J, Jackman A, Yuhas K. Circadian uses of melatonin in humans. Chronobiol Int. 2006;23(1-2):403-12.

Low Dog T, Riley D, Carter T. Traditional and alternative therapies for breast cancer. Alt Ther. 2001;7(3):36-47.

Lusardi P, Piazza E, Fogari R. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. Br J Clin Pharmacol. 2000;49(5):423-7.

Malhotra S, Sawhney G, Pandhi P. The therapeutic potential of melatonin: a review of the science. *Medscape General Medicine* 2004;6(2).

Moretti RM, Marelli MM, Maggi R, Dondi D, Motta M, Limonta P. Antiproliferative action of melatonin on human prostate cancer LNCaP cells. *Oncol Rep.* 2000;7(2):347-351.

Nagtagaal JE, Laurant MW, Kerkhof GA, Smits MG, van der Meer YG, Coenen AM. Effects of melatonin on the quality of life in patients with delayed sleep phase syndrome. *J Psychosom Res.* 2000;48(1):45-50.

Peled N, Shorer Z, Peled E. Pillar G. Melatonin effect on seizures in children with severe neurologic deficit disorders. *Epilepsia*. 2001;42(9):1208-1210.

Piccirillo JF. Melatonin. Prog Brain Res. 2007;166:331-3.

Pillar G, Shahar E, Peled N, Ravid S, Lavie P, Etzioni A. Melatonin improves sleep-wake patterns in psychomotor retarded children. *Pediatr Neurol.* 2000;23(3):225-228.

Ram PT, Yuan L, Dai J, Kiefer T, Klotz DM, Spriggs LL, et al. Differential responsiveness of MCF-7 human breast cancer cell line stocks to the pineal hormone, melatonin. *J Pineal Res.* 2000;28(4):210-218.

Reiter RJ. Melatonin: clinical relevance. Best Pract Res Clin Endocrinol Metab. 2003;17(2):273-85.

Sack RL, Brandes RW, Kendall AR, Lewy AJ. Entrainment of free-running circadian rhythms by melatonin in blind people. *N* Engl J Med. 2000;343(15):1070-1077.

Schernhammer E, Hankinson S. Urinary melatonin levels and breast cancer risk. *J Nat Canc Instit* 2005;97(14):1084-1087. Shamir E, Barak Y, Shalman I, Laudon M, Zisapel N, Tarrasch R, et al. Melatonin treatment for tardive dyskinesia: a doubleblind, placebo-controlled, crossover study. *Arch Gen Psych.* 2001;58(11):1049-1052.

Shamir E, Laudon M, Barak Y, Anis Y, Rotenberg V, Elizur A, et al. Melatonin improves sleep quality of patients with chronic schizophrenia. *J Clin Psychiatry*. 2000;61(5):373-377.

Simko F, Pechanova O. Potential roles of melatonin and chronotherapy among the new trends in hypertension treatment. *J Pineal Res.* 2009 Sep;47(2):127-33. Epub 2009 Jun 29. Review.

Smits MG, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. *J Child Neurol*. 2001;16(2):86-92.

Srinivasan V, Spence DW, Pandi-Perumal SR, Trakht I, Cardinali DP. Therapeutic actions of melatonin in cancer: possible mechanisms. *Integr Cancer Ther*. 2008 Sep;7(3):189-203. Review.

Stewart LS. Endogenous melatonin and epileptogenesis: facts and hypothesis. *Int J Neurosci*. 2001;107(1-2):77-85. van Wijingaarden E, Savitz DA, Kleckner RC, Cai J, Loomis D. Exposure to electromagnetic fields and suicide among electric

utility workers: a nested case-control study. West J Med. 2000;173;94-100.