Melatonin

And the quest for the holy grail, of a sleeping pill without side effects or dependency…

Lots of melatonin in use

According to the National Center for Complementary and Integrative Health, nearly 1.3 million American adults reported taking melatonin in February, 2015. Parents are even handing it out to their kids — 419,000 as of February — believing melatonin to be a harmless, naturally produced hormone.

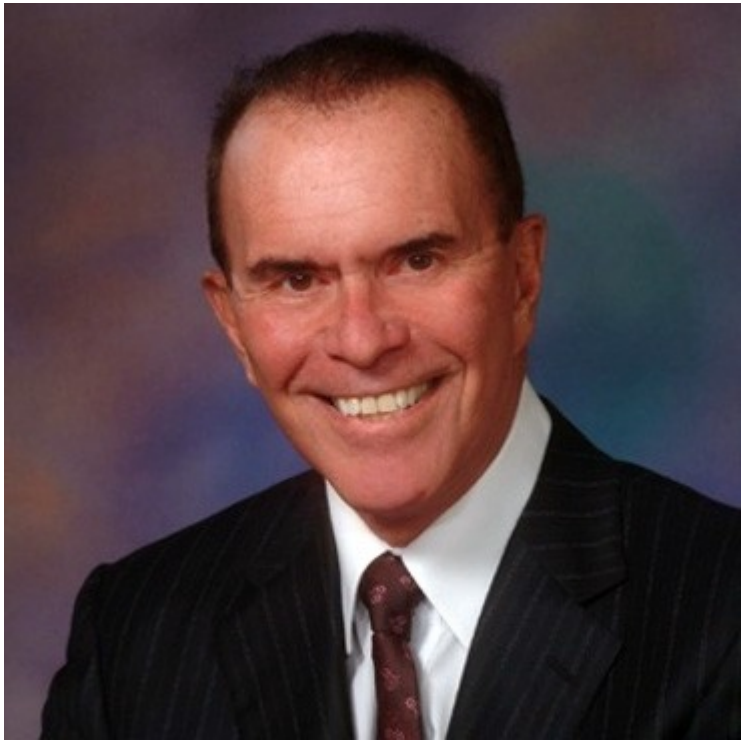
Melatonin is the number 1 over the counter sleep aid.

Melatonin sales continue to increase both in North America and globally.

In the United States, melatonin sales have risen from $285 million in 2016 to $821 million in 2020.

Richard Wurtman

"In 1994 his lab published work showing that melatonin is a hormone, secreted at night-time, needed for the induction & maintenance of normal sleep."
-- Wikipedia Article on Richard Wurtman



A Piece of Research On the Way to the Discovery

Science

1963 Nov 22;142(3595):1071-3. doi: 10.1126/science.142.3595.1071.

MELATONIN SYNTHESIS IN THE PINEAL GLAND: CONTROL BY LIGHT

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Abstract

In rats placed in continuous darkness for 6 days, there is a striking increase in the activity of melatonin-synthesizing-enzyme (hydroxyindole-0-methyl transferase) in the pineal gland, but no change in the activity of monoamine oxidase. Since melatonin appears to have a hormonal role in mammals, and its synthesis is confined to the pineal gland, the inhibition of hydroxyindole-O-methyl transferase by light may constitute a mechanism of neuroendocrine regulation.

Wurtman Study with Older Adults

"According to our research, the physiological dose of melatonin of about 0.3 milligrams restores sleep in adults over the age of 50," said Wurtman, lead investigator in the study. "The adults who would normally wake up during the second and third thirds of the night were able to sleep through the night with the 0.3 milligram dosage."

-- From MIT News

Continued

“The researchers also discovered that the typical health food store dosage of melatonin, which is about three milligrams (or 10 times the dosage in the study), is less effective in treating insomnia. In addition, the higher dosage can cause potentially serious side effects, including hypothermia (low body temperature). The study also showed that the higher dosage elevated plasma melatonin levels during the day, which can cause a "hangover" effect in some of the subjects.”

0.3 Mg dose also landed on by West Coast (Oregon) Chronobiology Researchers

We now report that lower (physiological) doses of up to 300 microg can entrain (synchronize) free-running circadian rhythms of 10 totally blind subjects that would otherwise drift later each day. The resulting log-linear dose-response curve in the physiological range adds support for a circadian function of endogenous melatonin in humans. Efficacy of exogenous doses in the physiological range are of clinical significance for totally blind people who will need to take melatonin daily over their entire lifetimes in order to remain entrained to the 24 h day. Left untreated, their free-running endocrine, metabolic, behavioral, and sleep/wake cycles can be almost as burdensome as not having vision.

Lewy AJ, Emens JS, Lefler BJ, Yuhas K, Jackman AR. Melatonin entrains free-running blind people according to a physiological dose-response curve. Chronobiol Int. 2005;22(6):1093-106. doi: 10.1080/07420520500398064. PMID: 16393710.

Theory of downregulation of receptors by exogenous melatonin

“When used occasionally and at the correct time, melatonin is a fine means of encouraging sleep. But, ironically, with prolonged use, it can actually amplify insomnia. Having too much melatonin in the system, the theory goes, overwhelms the receptors, changing how a patient reacts to the hormone — whether it’s endogenous or exogenous.

According to Dr. Wurtman, melatonin supplements may work at first, but soon “you’ll stop responding because you desensitize the brain. And as a consequence, not only won’t you respond to the stuff you take…you won’t respond to the stuff you make, so it can actually promote insomnia after a period of time.”

Grandner agrees. “Taking melatonin for an extended period of time your body may acclimate and re-adjust and produce less over time which will work against you.””

https://www.huffpost.com/entry/the-dark-side-of-melatoni_b_8855998

Example of the very scarce research on the question

Method: Five patients with rapid-cycling DSM-III-R bipolar disorder were treated with melatonin 10 mg q.d. at 10:00 p.m. for 12 weeks. Melatonin was added to a stable regimen of medication and administered in a double-blind, placebo-controlled fashion.

Results: Melantonin (sic) administration had no positive effects. One patient developed a free-running (unentrained) sleep-wake cycle after melatonin withdrawal. In addition, in both this and a second patient, there is evidence that the administration of exogenous melatonin may have suppressed the secretion of endogenous melatonin.

Leibenluft E, Feldman-Naim S, Turner EH, Wehr TA, Rosenthal NE. Effects of exogenous melatonin administration and withdrawal in five patients with rapid-cycling bipolar disorder. J Clin Psychiatry. 1997 Sep;58(9):383-8. doi: 10.4088/jcp.v58n0902. PMID: 9378688.

Evidence Feedback Control Melatonin

“We investigated the possibility of feedback control of melatonin by administering melatonin receptor antagonists to female white-footed mice and then measuring plasma melatonin concentrations. In the first experiment, we observed that luzindole, a dual MT1/MT2 receptor antagonist administered 1h after lights off, caused an increase in plasma melatonin both 1 and 2h later.”

Bedrosian TA, Herring KL, Walton JC, Fonken LK, Weil ZM, Nelson RJ. Evidence for feedback control of pineal melatonin secretion. Neurosci Lett. 2013 May 10;542:123-5. doi: 10.1016/j.neulet.2013.03.021. Epub 2013 Mar 23. PMID: 23528860.

Exogenous testosterone causes testicular atrophy and reduced sperm production – may or may not be reversible depending on how long given

Exogenous testosterone inhibits spermatogenesis by suppressing the HPG axis. Specifically, testosterone therapy results in negative feedback on the HPG axis. It inhibits gonadotropin-releasing hormone (GnRH), thereby inhibiting the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Fig. 1). Suppression of gonadotropins results in a decrease in intratesticular testosterone levels (ITT) and overall testosterone production. Normally, ITT concentrations are approximately 50 to 100 times serum levels. As exogenous testosterone therapies suppress ITT production, spermatogenesis can be dramatically compromised (6). Intratesticular testosterone is an absolute prerequisite for normal spermatogenesis, and its inhibition can result in azoospermia 7, 8.

Moss JL, Crosnoe LE, Kim ED. Effect of rejuvenation hormones on spermatogenesis. Fertil Steril. 2013 Jun;99(7):1814-20. doi: 10.1016/j.fertnstert.2013.04.003. Epub 2013 May 10. PMID: 23663992.

Ovaries reduced in size by BCP – appears fully reversible and not consequential

A study from Copenhagen University Hospital and Rigshospitalet shows that the ovaries are about 47 per cent smaller in women on the pill compared to women who don’t take the contraceptive.

"That the size of the ovaries is reduced so much is quite convincing," says lead author Kathrine Birch Petersen, fertility doctor and researcher at Rigshospitalet and Copenhagen University Hospital. "If we look at young women, between 19 and 29.9 years, their ovaries are reduced by 52 per cent compared with women who are not on the pill."

She stresses that the phenomenon is not dangerous and that the ovaries appear to return to normal size in the months after the woman stops taking the pill.

From a doctor’s website, about thyroid hormone

Once you start taking thyroid medication (of any dose) it causes a negative feedback loop in your brain which REDUCES the amount of thyroid hormone that your thyroid gland produces naturally. This is a natural and healthy mechanism that is put in place by your body to prevent too much thyroid hormone from being produced. But the problem is your body doesn’t necessarily know the difference between thyroid medication that you take by mouth or thyroid hormone that your thyroid gland produces naturally. So once it sees any thyroid hormone it alters the signals that it sends to your thyroid gland by lowering the TSH. The more thyroid medication you take by mouth the lower your TSH will get. So, as you stop taking your thyroid medication, it’s only natural that this TSH will start to increase. But you have to be aware of one major important point. Once your TSH has been artificially lowered with thyroid medications, it takes time for your brain and pituitary system to get back to full strength. In fact, it can take several weeks to months for it to get back to the normal state you were in prior to taking thyroid medication. Because of this, there will be a short period of time where your body isn’t producing enough thyroid hormone on its own (because it can’t) and where you are not taking enough thyroid medication by mouth to supplement this difference. During this transition period, it’s normal, therefore, for you to feel bad! Because you don’t have sufficient thyroid hormone in your body. This by itself isn’t a reason to think that you have to be on thyroid medication, however. But, if your body doesn’t get back to normal and if you aren’t feeling well after 2-3 months, then you may be someone who has permanent thyroid damage and will be required to take thyroid medication indefinitely.

Is the dose labeled on the supplement accurate?

This study quantified melatonin in 30 commercial supplements, comprising different brands and forms

Results: Melatonin content was found to range from -83% to +478% of the labelled content. Additionally, lot-to-lot variable (sic) within a particular product varied by as much as 465%. This variability did not appear to be correlated with manufacturer or product type.

Erland LA, Saxena PK. Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content. J Clin Sleep Med. 2017 Feb 15;13(2):275-281. doi: 10.5664/jcsm.6462. PMID: 27855744; PMCID: PMC5263083.

Meta-Analysis of Efficacy of Melatonin as a Sleeping Pill

“The analysis used information derived from 17 different studies (involving 284 subjects) that satisfied inclusion criteria. Sleep onset latency, total sleep duration, and sleep efficiency were selected as the outcome measures. The study effect size was taken to be the difference between the response on placebo and the mean response on melatonin for each outcome measured. Melatonin treatment significantly reduced sleep onset latency by 4.0 min (95% CI 2.5, 5.4); increased sleep efficiency by 2.2% (95% CI 0.2, 4.2), and increased total sleep duration by 12.8 min (95% CI 2.9, 22.8).

Sleep Med Rev, . 2005 Feb;9(1):41-50. doi: 10.1016/j.smrv.2004.06.004. Effects of exogenous melatonin on sleep: a meta-analysis. Amnon Brzezinski 1, Mark G Vangel, Richard J Wurtman, Gillian Norrie, Irina Zhdanova, Abraham Ben-Shushan, Ian Ford

A different nominee for the holy grail:

From a randomized study with adults over 55:

Results: The ??? group improved in sleep quality on the global PSQI ($p<.0001$), sleep latency ($p=.049$), sleep duration ($p=.04$), daytime dysfunction ($p=.027$), and sleep efficiency ($p=.036$) PSQI sub-scores compared to the control group. The ???
group also had reductions in depressive symptoms ($p=.044$), daytime sleepiness ($p=.02$) and improvements in vitality ($p=.017$) compared to baseline scores.

Answer to the guessing game

??? = Exercise