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COMMENTARY

Physiological Effects of Melatonin in Children

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Melatonin Overview

Melatonin is a hormone produced in the body that affects when a person sleeps [1]. It contains 16 hydrogen atoms, 13 carbon atoms, 2 nitrogen atoms, and 2 oxygen atoms (C13H16N2O2) [2]. The hormone gets produced in the pineal gland located in the brain. The hormone is then shot into the bloodstream [3]. Depending on whether there is light (day) or darkness (night), the levels of melatonin increase and decrease [1]. Sometimes, however, the melatonin levels at night can be low, making it difficult to fall asleep. This causes people to rely on a melatonin supplement that helps increase their melatonin levels. This supplement comes in various forms that can be bought over the counter. For instance, you can find them as forms of pills, drops, sprays, and gummies. In addition, you can either get this supplement natural or synthetic. However, the natural form is made in pineal glands from animals that can be contaminated by viruses during the extraction, while synthetic is manmade and does not carry the same risk. [4].

Melatonin Use

Melatonin is utilized by many different people for a variety of reasons. According to the CDC, a 10-year period study by the American Association of Poison Control Centers' National Poison Data System reported that the yearly number of melatonin intake increased by 530% with 260,435 pediatric melatonin ingestions announced [5]. However, melatonin is not only utilized in children; it can also be prescribed and used by adults in order to aid in problems involving short-term sleep.

Moreover, in the United States, the purchase and intake of melatonin doubled between 2007- 2012, making it the 4th most natural product consumed by adults and 2nd most natural product consumed by children [6]. Melatonin's popularity is continuously growing due to the fact that it can be used to regulate sleep cycles where the creation of melatonin is influenced by the specific time of day. Melatonin supplements can also be utilized to help in withdrawal from benzodiazepines and in decrease of blood pressure [7].

In addition, there are even specific diseases that require melatonin use in order to help the individual who has acquired that disease. For instance, as stated by the Mayo Clinic, melatonin can be utilized to benefit and improve insomnia for older adults by decreasing the individual's ability to fall asleep, regulating circadian rhythm sleep disorders in the blind in children and adults, and jet lag symptoms by enhancing attentiveness and tiredness during the day [1]. Furthermore, melatonin is extremely effective and can even be used to improve and reduce the pain of a uterine disorder known as endometriosis in adults by taking melatonin orally [8].

Melatonin Prescriptions

Melatonin is prescribed by doctors to treat circadian rhythm disorders, and to provide relief for insomnia [9]. It may also be used to substitute the hormone for patients who are

Melatonin deficient throughout the night [10]. Another reason that doctors may be prescribing it is to help with anxiety before or after surgery [9]. Researchers have found that the prescribing of melatonin for hospitalized patients has increased substantially over a 4-year period, despite limited research on dosing, [11].

Beneficial and Adverse Outcomes of Melatonin Use

Parents administer melatonin to children and/or teenagers to help them get to a more relaxed state before bed. However, melatonin is already naturally produced. Although there is no real evidence of overdosing on melatonin, it is still a risk [12]. Anytime a child ingests melatonin, they run the risk of experiencing certain side effects. For example, nausea, vomiting, headaches, hypotension or hypertension [12,13]. A long-term health risk from melatonin has not been found since there is a lack of high-quality studies in the U.S. However, increased use of melatonin at the pediatric stage can lead to multiple disorders [13]. For example, cardiac disorders, circadian rhythm, delay sexual maturation, and depression. Although there are certain downfalls when using OTC Melatonin, there are also some positives. According to new research, melatonin has been shown to synchronize the circadian rhythms, and improve the onset, duration and quality of sleep [14]. Every year the number of overdoses involved with melatonin have increased dramatically [9]. According to a study conducted, the number of reports to U.S. poison control centers about people 19 years and younger who took melatonin increased from 8,337 in 2012 to 52,563 in 2021 [9].

Adverse Effects of Melatonin Use

Pulmonary Hypertension

Pulmonary hypertension in children is caused by congenital heart defects present at birth [16]. Pulmonary hypertension is narrowed, blocked, or destroyed blood vessels in the heart which causes high blood pressure that affects arteries in the lungs and the right side of the heart while simultaneously causing blood clots, arrhythmia, and bleeding in the lungs [17]. It also inhibits the body's natural production of melatonin. Melatonin supplements are shown, in recent studies, to have lowered the severity of pulmonary hypertension, helping to prevent chronic hypoxia caused by Pulmonary Hypertension, and also have anti-inflammatory effects, which inhibits oxidative stress, restoring nitric oxide production. In a study conducted through 2014 - 2019, 64 adult patients, 43 patients diagnosed with Pulmonary Arterial Hypertension and 21 patients diagnosed with Chronic Thromboembolic Pulmonary Hypertension, and 111 individuals who reported themselves as healthy were used to test the positive and negative effects of melatonin in their cardiovascular and respiratory health, under the accordance of the Declaration of Helsinki. Consistent blood sampling was performed during each scheduled visit, between the times of 9:00 and 18:00, where the natural melatonin levels in the blood were expected to be stable. Blood samples would then be frozen and stored in aliquots at -80c and then thawed only once for use.

Melatonin levels were measured using ultra-performance liquid chromatography-tandem mass spectrometry. The results obtained from these tests help show the difference in melatonin levels in the patients. Overall, the research came to the conclusion that individuals who have been diagnosed with PAH or CTEPH have an independent risk factor of PAH in logistic regression analysis while individuals who have lower levels of melatonin were predicted to have a worse long-term survival rate [15].

Valvular Heart Disease

Melatonin inhibits NF-KB/Creb/ Runx2 that stimulates and increases aortic valve calcification [18]. It causes a high mortality rate. (many deaths) This study showed that the use of melatonin signals valvular interstitial cell calcification of the aortic valve, leading to aortic valve disease.

Aortic calcification is a disease in which calcium deposits form on the aorta and most commonly the Aortic valve. This causes narrowing also known as stenosis thus causes reduced blood flow, this poor blood perfusion and circulation that may often cause medical issues and increases the risk of death [19].

Delay in Sexual Maturation

Melatonin may affect the length of one's ovulation cycle and may affect menopause as well [20]. The use of long term melatonin (2 or more years) will delay one's sexual maturity. Long term use of melatonin delays sexual maturity by interrupting the decline in melatonin levels that occur at night and on the beginning of puberty [21].

There are many different studies that show the correlation in sexual maturation and melatonin use in adolescent individuals. In a recent research study animal studies showing the exogenous melatonin can suppress GnRH secretion [21]. GnRH secretion is responsible for sexual development, ovulation cycles, and regulating the onset of puberty. Suppression of this hormone can produce pubertal disorders indicating this may affect a child's sexual maturation [22].

Interactions between Melatonin and Other Medications and Herbal Remedies

Through research, the effects of melatonin along with other medications and herbal remedies are shown to increase the risk of situations to worsen. For example, anticoagulants, anti-platelet, and herbs are medicines used to reduce blood clotting. However, when these drugs combine with melatonin it could increase the risk of bleeding. Furthermore, the use of melatonin along with blood pressure drugs and diabetes medications might affect blood pressure and sugar levels. As a result, the adverse effects melatonin has with medicine can lead to many problems [1].

Current Research

Melatonin can be used to help women, who have breast cancer, to help slow the growth of cancer cells. Several studies have shown it can also increase the risk of side effects of chemotherapy drugs (that are used to help treat cancer) including loss of appetite, nausea, diarrhea, hair loss, a change in the muscles (muscle strain and loss of strength), nerve (numbness and pain in thumbs and toes), and hearing (loss in hearing), and increased risk of infections. However, melatonin can also have an opposite effect on medication [23]. Although the use of melatonin can help benefit people with different problems like breast cancer, it could also interfere with medications causing them to either "cancel out" the medication or to make the medication more "powerful". For instance, in type 2 diabetics, they take a medication called metformin that is used to help the body regulate blood sugar levels. (NHS) However, when people with type 2 diabetes take melatonin, the melatonin levels do increase, but the melatonin reduces the ability for the insulin to create more insulin causing it hard to regulate blood sugar levels. This results in the pancreas working harder to produce enough insulin for the glucose [25]. A different study shows that melatonin can have an effect on diabetes medications. In recent studies, melatonin has many effects on pancreatic B-cells (cells that release insulin that plays a key role in glucose regulation). Non-functional pancreatic B-cells lead to uncontrolled blood glucose levels and diabetes. Pancreatic B-cells are susceptible to oxidative stress which reduces the function or survival of B-cells. However, melatonin can provide protection against it and help balance the amount of insulin produced [24].

Conclusion

Overall, melatonin is used to help children receive the recommended amount of sleep and provide parents with relief, however, numerous studies have shown that the use of melatonin in the pediatric population can carry cons such as causing unwanted side effects like nausea, loss of appetite, delay in sexual maturation, and worsening of chronic disease symptoms. On the contrary to the effects melatonin has with other medications, it is also shown to help improve various medicines to treat diseases. For example, the many research studies that have gone into finding a proper treatment for Covid-19. As Covid-19 has been on the watch list for many doctors, researchers have found vitamin C and D work efficient against Covid-19. Since, vitamin C helps the body with its healing process along with increasing the anti-oxidative (Oxidative damages cells, proteins, and DNA function, and vitamin D helps with the immune system. Combining them with melatonin, vitamin C defense against oxidative and vitamin D immune systems improve [28].

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