Researchers propose guidelines for the therapeutic use of melatonin

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In an article published in Endocrine Reviews, Brazilian professors discuss the general criteria to be considered when prescribing the pineal hormone as a health supplement . Credit: Murrur / Wikimedia

Sixty years after melatonin was isolated and with more than 23,000 published studies showing the many functions of this hormone secreted by the pineal gland, guidelines should be discussed and established for its therapeutic use.

This is the view expressed by José Cipolla Neto, Full Professor at the University of São Paulo's Biomedical Science Institute (ICB-USP), and Fernanda Gaspar do Amaral, a professor at the Federal University of São Paulo (UNIFESP), both in Brazil, in an article published in the journal *Endocrine Reviews*.

Cipolla Neto is the principal investigator for a project supported by São Paulo Research Foundation—FAPESP on the role of melatonin in energy metabolism regulation.

"Melatonin not only adapts the organism to nocturnal rest but also prepares it metabolically for the next day, when it will need to be sufficiently sensitive to absorb food, for example," he said. The body produces melatonin only at night.

"If the nocturnal production of melatonin is blocked by light during the night, especially by the blue light from smartphones, this can contribute to diseases, such as sleep disorders and hypertension, and metabolic disturbances, including obesity and diabetes. This potentially pathogenic situation is due not only to insufficient melatonin production but also to one of its more immediate consequences, which is a condition known as chronodisruption, a temporal disorganization of the circadian rhythm of biological functions," Cipolla Neto said.

Melatonin has been the focus of many clinical studies. In the last five years alone, more than 4,000 studies using melatonin have been published. Almost 200 of those were randomized clinical trials.

Between 1996 and July 2017, for example, 195 systematic reviews were published on the effects of the clinical use of melatonin, among which 96 addressed the use of melatonin to treat psychiatric diseases and neurological disturbances, including sleep disorders, while 43 focused on the association between melatonin and cancer.

Patent applications relating to therapeutic uses of melatonin and analogs filed worldwide between 2012 and September 2014 focused predominantly on the central nervous system—including sleep disorders, the disruption of the circadian cycle and neuroprotection—as well as cancer and immunological issues.

In spite of the impressive amount of data on melatonin and the pineal gland, researchers and clinicians lack a systematic standard theoretical framework of analysis that could assist in the appropriate interpretation of the data obtained and the development of an adequate understanding of the role played by melatonin in human physiology and pathophysiology, according to the authors of the article, who say their intention is "to propose a framework of analysis that would help researchers and health professionals to analyze, understand and interpret the effects of melatonin and its putative role in several pathologies."

Individual variation

Characterized chemically in 1959, melatonin—which derives from tryptophan, an essential amino acid found in proteins—is highly efficient at eliminating free radicals and has remarkable antioxidant properties. It interacts directly with free radicals and stimulates antioxidant enzymes in different tissues.

This role has long been proposed as melatonin's primary function; however, in recent years, researchers have discovered that owing to its special properties, it is an exceptionally important molecule that acts through several mechanisms at almost all physiological levels. These include all components of the cardiovascular, reproductive, immune, respiratory and endocrine systems as well as energy metabolism, according to the authors.

"Melatonin's modes of action and integrative role amplify and diversify

its functional activities, particularly in the time domain, enabling the organism's physiology to deal with challenges present while it's being secreted by the pineal gland, and at the same time preparing the organism for future events. Similarly, melatonin synchronizes our organism's temporal order both daily and on the seasonal time scale," Cipolla Neto said.

"Consequently, all these particular modes of action should always be taken into consideration in both laboratory experiments [in cells] and animals, and especially in clinical studies and investigations into the use of melatonin as a treatment. In this case, above all, it should be kept in mind that melatonin's effects depend not just on the route of administration and concentration but also on the time of administration, among other factors."

In addition, it is important to consider that the profile and onset of melatonin production vary from person to person. Early birds (people who wake early) start their daily melatonin production before night owls (people who stay up late), and people who sleep for longer periods of time produce melatonin over a longer time than those who sleep for shorter periods.

Furthermore, according to the researchers, it should be kept in mind that a given dose of melatonin may result in different plasma levels in different patients owing to individual differences in absorbing, distributing, metabolizing and eliminating melatonin. These differences are associated with age, clinical condition, the existence of pathologies, and the functional integrity of physiological systems such as the gastrointestinal tract, liver and kidneys.

If these substantial differences are not adequately taken into account, they may impact clinical efficacy, the authors state, adding that "a proper chronic melatonin hormonal replacement therapy is only

achieved when dosage and formulation are carefully chosen and individually tailored and controlled to accomplish the desired clinical effect."

The first and most important guideline for the clinical use of melatonin proposed by the authors is to determine the duration of the daily signal and the start of production in each patient and then to prescribe melatonin according to this reference point in time, called the dim light melatonin onset (DLMO).

This specific point on the daily melatonin production curve is an important temporal reference for the proper administration of the hormone to patients. Depending on the time at which it is administered—always using the DLMO as a guide—exogenous melatonin may advance, delay or have no effect on the timing of endogenous circadian rhythms.

Because the procedure to determine DLMO is typically not feasible in everyday clinical practice, a more practical approach is to take the time at which the patient usually goes to sleep at night as a reference for the timing of melatonin administration.

According to the authors, most oral formulations require approximately 45 minutes to an hour to become bioavailable, so a dose should be taken about an hour before the usual reported bedtime. Given that melatonin is a powerful timer of the organism's physiology, it should be taken strictly at the same time every day.

Dose is another key point to be discussed. There is no consensus in the literature on this matter. On average, plasma levels in young people who take 0.1-0.3 milligrams will reach 100-200 picograms per milliliter (pg/ml), equivalent to the expected normal physiological range, while 1 gram will probably result in plasma levels of 500-600 pg/ml, which is

much higher than the physiological range.

In their concluding summary, the authors note that the following precautions should be taken into consideration in melatonin therapy: chronic administration should be restricted to nighttime, the time should be carefully chosen according to the desired effect, and the dose and formulation should be individually adapted to build a blood melatonin profile that mimics the physiological ideal, ending by early morning.

More information: José Cipolla-Neto et al, Melatonin As A Hormone: New Physiological And Clinical Insights, *Endocrine Reviews* (2018). DOI: 10.1210/er.2018-00084

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