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COMMENTARY

Poor Quality Control of Over-the-Counter Melatonin: What They Say Is Often Not What You Get

Commentary on Erland and Saxena. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. *J Clin Sleep Med.* 2017;13(2):275–281.

Madeleine M. Grigg-Damberger, MD[1,2]; Dessislava Ianakieva, MD[3]

[1]Department of Neurology, University of New Mexico School of Medicine, Albuquerque, NM; [2]Pediatric Sleep Services, University of New Mexico Sleep Disorders Center, Albuquerque, NM; [3]University of New Mexico Sleep Disorders Center, Albuquerque, NM

Between 2007 and 2012 over-the-counter (OTC) melatonin use in United States adults more than doubled, with a reported 3.1 million individuals (1.3%) taking the drug in 2012.[1] Melatonin is the fourth most popular natural product taken by United States adults (after fish oil/omega 3-fatty acids, glucosamine/chondroitin, and probiotics).[1] Melatonin is the second most popular natural product used by children in the United States (second only to fish oil), increasing from 0.1% in 2007 to 0.7% (419,000) in 2012.[1]

The global market for melatonin (valued at $504 million in 2012) is expected to double by 2019.[2] The United States is its largest market; sales of melatonin in the United States increased by more than 500% between 2003 and 2014 ($62 to $378 million).[2] The question is why? OTC melatonin has been banned for years in the United Kingdom (UK), European Union, Japan, Australia and most recently Canada. Exogenous melatonin is not outlawed by these countries but regarded as a medicine, available only by prescription. In the UK and Australia melatonin is approved for the short-term treatment of primary insomnia in adults older than 55 y. In the UK, melatonin with prescription is approved for treatment of some sleep disorders in children with neurological disorders; doses of 2 to 10 mg are permitted but require review for continued use every 6 mo.

In this issue of the *Journal of Clinical Sleep Medicine*, Erland and Saxena systematically analyzed the actual melatonin content (and presence of contaminants) in 31 melatonin supplements purchased from groceries and pharmacies in one city in Canada (before countrywide OTC use of it in Canada was banned). Their findings herald what may also be true in OTC melatonin supplements marketed in the United States. Melatonin content varied from an egregious −83% to +478% of labeled melatonin and 70% had melatonin concentration ≤ 10% of what was claimed. Worse yet, the content of melatonin between lots of the same product varied by as much as 465%.[3]

The most variable sample was a chewable tablet (and most likely to be used by children). It contained almost 9 mg of melatonin when it was supposed to contain 1.5 mg and also exhibited the greatest variability between lots (465% difference). The lowest melatonin content was −83% compared to its labeled value in a capsule that also contained lavender, chamomile, and lemon balm. Capsules showed the greatest variability between lots. Liquid supplements surprisingly showed generally high to median stability with low lot-to-lot stability. The least variable products were those that contained the simplest mix of ingredients, generally oral or sublingual tablets with melatonin added to a filler of silica or cellulose derivatives and were the most reproducible. The last disturbing finding was more than a quarter of melatonin products contained serotonin, some at potentially significant doses. Serotonin is a breakdown product of melatonin metabolism but could have medicinal effects and should be taken without oversight. In short, there was no guarantee of the strength or purity of OTC melatonin.

Does the dose of melatonin received matter? Lower doses might be ineffective, night-to-night variability in dose interpreted as secondary failure of efficacy, and higher doses could lead to unpleasant/unexpected side effects, particularly for those who are sensitive to it or taking medications that show drug interactions with melatonin, and in those who are pregnant, allergic to the impurities, or have diabetes/prediabetes. The long-term effects of melatonin supplementation on prepubertal children remain unknown.[4,5]

Few know that melatonin in the early 1960s was known as an antigonadal hormone.[5] Doses as little as 1 µg (20 µg/kg) reduced gonadal size and fertility in various rats, mice, and hamsters. Doses well below those used in children had physiological effects on gonadal function in rodents and primates; for children a 3-mg tablet of melatonin equals 200 µg/kg for a 15-kg child, and equals 60 µg/kg for a child weighing 50 kg. Melatonin implants in cats inhibit estrus and advanced the onset of puberty in primates by 5 mo. According to the study by Reiter,[6] to assume melatonin would not have some sexual effects in humans would almost seem naïve.

The authors were not particularly surprised by decreased actual melatonin content in many melatonin products because of well-known degradation or stability issues.[7] However, they found the excessive melatonin content puzzling, and pondered whether excessive melatonin was added to ensure the product met the label claim. The researchers declined to name the

products or manufacturers, which probably was wise because not one stood out among them (avoiding arguments and suits from manufacturers).

We celebrate the medicinal benefits of melatonin as chronobiotic for particular patient populations, sleep disorders, and medical conditions. The American Academy of Sleep Medicine recommended melatonin to treat delayed sleep/wake phase disorder, blind adults with non–24-h sleep/wake disorder, and irregular sleep/wake disorders in children or adolescents with neurological disorders.[8] Melatonin reduces dream behavior enactment and lessens rapid eye movement sleep without atonia in older patients with chronic rapid eye movement behavior disorder.[9,10] Melatonin can be beneficial in improving chronic sleep onset insomnia in children with autism spectrum disorders.[11,12] Research studies continue to explore therapeutic uses for exogenous melatonin harnessing its power as antioxidant,[13,14] reducing intrauterine growth restriction,[15] and improving sleep quality in patients with cancer.[16,17] Melatonin appears to inhibit nocturnal insulin release,[18] and long-term use of prolonged-release melatonin in patients with type 2 diabetes mellitus had a beneficial effect on their hemoglobin A1c levels.[19] Studies are underway exploring whether melatonin provides neuroprotection in stroke[14] and lessening delirium in intensive care unit patients.[20]

It would be worthwhile for this study to be reproduced using OTC melatonin products sold in the United States, given the continuing unrestricted rise in its use. We need to remind ourselves (and our patients) that oral melatonin is rapidly absorbed with peak levels 20 to 30 min after oral ingestion (T_{max}) but a very short elimination half-life ($t_{1/2}$) of only 40 to 60 min.[21] Melatonin works best as a chronobiotic, not a hypnotic, agent. A recent meta-analysis of 17 studies (mostly healthy subjects) showed melatonin shortened sleep latency by a mean of 4 min, increased sleep efficiency by 2.2% and lengthened sleep duration by 12.8 min; all values are modest at best.[22]

Oral melatonin has poor and variable bioavailability. Recent research studying alternative routes for it find high plasma concentrations can be achieved with oral transmuscosal melatonin while avoiding first-pass metabolism of it.[23] Intranasal melatonin exhibits rapid absorption and high bioavailability. However, transdermal or subcutaneous injection of melatonin show variable and often slow absorption and possible skin deposition, and little advantage. Studies are needed to identify the best indications, routes of administration, and doses for exogenous melatonin.

This well-designed pharmacological study from our northern neighbors showing that the content and purity of OTC melatonin is suspect prompts us to again request that the United States Food and Drug Administration regard melatonin as a medicine, and use all its forces to regulate it, and restrict its use to prescription-only.

CITATION

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Address correspondence to: Madeleine M. Grigg-Damberger, MD, Professor of Neurology, Department of Neurology, University of New Mexico School of Medicine, Medical Director, Pediatric Sleep Services, University of New Mexico Sleep Disorders Center, The University of NM, 1 University of New Mexico, MSC10 5620 Albuquerque, NM 87131-0001; Tel: (505) 272-3342; Fax: (505) 272-6692; Email: mgriggd@salud.unm.edu

DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.