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Supporting Sleep, Stress, and Immune Health in the Pharmacy

EMERGING EVIDENCE SUPPORTS THAT THE COVID-19 pandemic introduced many unique challenges in health care, negatively affecting Americans' mental health, stress levels, and sleep hygiene. In an analysis of survey data collected from the National Health Interview Survey aimed to assess the implications of the COVID-19 pandemic on mental health and well-being, there was a 4-fold percentage increase in adults who self-reported symptoms of anxiety and/or depressive disorders from January 2019 to January 2021 (11% vs 41%).^{1,2}

For many Americans, the COVID-19 pandemic has induced feelings of anxiety and stress, which can adversely affect sleep. In a July 2020 survey conducted by the Kaiser Family Foundation, 36% of adults reported that they have trouble sleeping due to worry and stress over the pandemic.³ Results from a separate survey conducted in May 2020 showed that 89% of adults self-reported changes to their sleeping habits since the start of the COVID-19 pandemic, including going to bed later (77%), sleeping less (45%), sleeping more in front of a screen (52%), and using screens more often in the bedroom (62%).⁴ Given the relationships among sleep, stress, and immune health, pharmacists can discuss the potential use of safe and effective dietary supplements with synergistic ingredients that support sleep, mood, and immunity to promote overall well-being.

ADDRESSING NUTRIENT SHORTFALLS

Ongoing research that explores the interconnectivity of sleep, stress, and immune health has suggested that nutrition plays an important role in maintaining overall health, and where vitamins and other dietary supplements can help fill potential nutrient gaps. Inadequate nutrient intake, or shortfalls of common essential nutrients, is a persistent challenge, with increasing prevalence in the last decade.

Nutrient shortfalls can affect sleep, stress, mood, and immunity, becoming a risk factor for poor or fair overall health.⁵⁻⁸ In a National Health and Nutrition Examination Survey (NHANES) data analysis (2005–2016), short sleep duration was shown to be associated with nutrient inadequacy. In adults aged 19 years and older who reported short sleep (<7 hours) duration, shortfall micronutrients (lower

than usual intake from food and supplements) included calcium, magnesium, and vitamins A, C, and D. Adults from 51 to 99 years of age had a higher prevalence of those same nutrient shortfalls plus shortfalls of vitamins B₆, E, and zinc, which were also associated with short sleep duration.⁹ An additional analysis of NHANES data (2005–2016) identified the prevalence of inadequate immunity-supportive nutrient intake in the US population of vitamin A (45%), vitamin C (46%), vitamin D (95%), vitamin E (84%), and zinc (15%).⁵

This evidence emphasizes an opportunity for filling nutrient gaps with dietary supplementation of synergistic nutrients and ingredients that may help with desired sleep, stress, and immune health outcomes.

SLEEP AND STRESS

Many sleep aids and dietary supplements that support sleep are available in the pharmacy that contain melatonin, an ingredient that can aid in falling and staying asleep and may be beneficial for a healthy sleep hygiene routine.¹⁰ Additional ingredients that provide support leading to the desired benefits of reduced stress and improved mood may be warranted, creating an opportunity to incorporate supplements with ingredients that help relax the mind and include melatonin for sleep health.

L-Theanine

L-theanine supports a calm mind, reduces anxiety, and promotes relaxation by acting on alpha waves—one of 4 main types of brain waves in the adult brain that can define various mood states—and inducing resting state activity.^{11,12} Results from several clinical studies have supported the effects of *L*-theanine in its synthetic and natural forms to help relax the mind.¹²⁻¹⁶ Individuals with anxiety can have a stress state that is driven and perpetuated by high levels of the hormone cortisol.^{17,18} Alpha wave activity is inversely correlated with cortisol levels; as alpha waves become predominant, cortisol levels decrease. *L*-theanine administration has been shown to reduce cortisol levels.^{17,18}

B Vitamins

Other synergistic ingredients may act together within the stress, sleep, and mood continuum to increase serotonin

that is later converted to melatonin. There is evidence that suggests high doses of B vitamins may be a potential strategy to improve mood. In a meta-analysis of data collected from 8 randomized, placebo-controlled studies that investigated aspects of stress, mild psychiatric symptoms, or mood in the general population by evaluating the influence of multivitamin/mineral supplements for at least 28 days, adults who consumed higher levels of B vitamins had a significant reduction in stress ($P = .001$).¹⁹

SLEEP AND IMMUNITY

Sleep is an integral part of maintaining immunity. Irregular or insufficient sleep quality and duration can contribute to the deregulation of inflammatory and antiviral responses of the immune system.²⁰ For those with sleep deficiencies, melatonin combined with known vitamins and minerals may help support overall immune health.

Vitamin D

Best known for its role in bone health, vitamin D supports different aspects of immune function, and research supports its importance for overall health. Vitamin D can help modulate the immune responses to antigens in addition to increasing expression of cathelicidin, an antimicrobial peptide that is important for the innate immune system. Vitamin D deficiency affects both innate and adaptive immune systems.^{21,22}

Zinc

Inadequate zinc intake has many adverse effects on the immune system. Severe zinc deficiency depresses immune function.²³ Mild to moderate degrees of zinc deficiency can impair macrophage and neutrophil functions, natural killer cell activity, and complement activity.²⁴ Additionally, zinc helps inhibit the production of reactive oxygen species, provides essential antioxidant support, and neutralizes free radicals.²⁵

Vitamin E and Vitamin C

Vitamin E and vitamin C also support immune health through neutralizing free radicals created by oxidative stress, an effect that is likely enhanced by the combination of these vitamins. Vitamin E is found in high concentrations in immune cells and is thought to protect against oxidative damage to polyunsaturated fatty acids in the membrane. Vitamin C scavenges oxygen radicals and can protect lung cells against oxidant-mediated damage caused by pollutants.^{26,27}

ROLE OF THE PHARMACIST

As COVID-19 restrictions are lifted and many Americans are returning to work, pharmacists may have an opportunity to support consumers who come to the pharmacy looking for an immune-supportive supplementary option as well as support for stress, mood balance, and sleep health. Pharmacists can work with consumers to help them understand their sleep-support needs and encourage them to follow good sleep habits.

In response to the mental health, stress level, and sleep hygiene challenges introduced by the COVID-19 pandemic, the Sleep Foundation has issued revised guidelines that provide several sleep habits and tips.²⁸ Pharmacists can advise those with irregular sleeping patterns to eat healthy meals at the same time each day, maintain a regular sleep schedule (waking up and going to sleep at the same time daily), relax before bedtime, avoid stimulants such as caffeine and nicotine, and establish a good sleep environment that is free of distractions.²⁸ Given the prevalence of several nutrient shortfalls, pharmacists can advise on the importance of dietary supplements to address nutritional deficits.

For those who are still unable to meet their sleep needs, pharmacists can discuss the potential use of safe and effective dietary supplements that are available in the pharmacy and increase awareness of supplements formulated with melatonin and other synergistic ingredients. ■

References are available on [PharmacyTimes.com](https://www.pharmacytimes.com).

REFERENCES

- National Center for Health Statistics. Estimates of mental health symptomatology, by month of interview: United States, 2019. March 2021. Centers for Disease Control and Prevention. Accessed August 2, 2021. <https://www.cdc.gov/nchs/data/nhis/mental-health-monthly-508.pdf>
- National Center for Health Statistics. Anxiety and depression. Household Pulse Survey. Centers for Disease Control and Prevention. Last updated July 14, 2021. Accessed August 1, 2021. <https://www.cdc.gov/nchs/covid19/pulse/mental-health.htm>
- Panchal N, Kama R, Cox C, Garfield R. The implications of COVID-19 for mental health and substance use. Kaiser Family Foundation. February 10, 2021. Accessed August 2, 2021. <https://www.kff.org/coronavirus-covid-19/issue-brief/the-implications-of-covid-19-for-mental-health-and-substance-use/>
- Coiro MJ, Asraf K, Tzischinsky O, Hadar-Shoval D, Tannous-Haddad L, Wolfson AR. Sleep quality and COVID-19-related stress in relation to mental health symptoms among Israeli and U.S. adults. *Sleep Health*. 2021;7(2):127-133. doi:10.1016/j.sleh.2021.02.006
- Reider CA, Chung RY, Devarshi PP, Grant RW, Mitmesser SH. Inadequacy of immune health nutrients: intakes in US adults, the 2005-2016 NHANES. *Nutrients*. 2020;12(6):1735-1735. doi:10.3390/nu12061735
- USDA. Scientific Report of the 2015 Dietary Guidelines Advisory Committee: NHANES 2005-2008. US Department of Health and Human Services. February 2015. Accessed August 2, 2021. <https://health.gov/sites/default/files/2019-09/Scientific-Report-of-the-2015-Dietary-Guidelines-Advisory-Committee.pdf>
- Murphy RA, Devarshi PP, Ekimura S, Marshall K, Mitmesser SH. Long-chain omega-3 fatty acid serum concentrations across life stages in the USA: an analysis of NHANES 2011-2012. *BMJ Open*. 2021;11(5):e043301. doi:10.1136/bmjopen-2020-043301
- Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients*. 2020;12(1):236. doi:10.3390/nu12010236
- Ikonte CJ, Mun JG, Reider CA, Grant RW, Mitmesser SH. Micronutrient inadequacy in short sleep: analysis of the NHANES 2005-2016. *Nutrients*. 2019;11(10):2335. doi:10.3390/nu11102335
- Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS One*. 2013;8(5):e63773. doi:10.1371/journal.pone.0063773
- Williams J, McKune AJ, Georgousopoulou EN, et al. The effect of L-theanine incorporated in a functional food product (mango sorbet) on physiological responses in healthy males: a pilot randomised controlled trial. *Foods*. 2020;9(3):371. doi:10.3390/foods9030371
- Juneja LR, Chu DC, Okubo T, Nagato Y, Yokogoshi H. L-theanine—a unique amino acid of green tea and its relaxation effect in humans. *Trends Food Sci Technol*. 1999;10(6-7):199-204. doi:10.1016/S0294-2244(99)00044-8
- Song CH, Jung JH, Oh JS, Kim KS. Effects of theanine on the release of brain alpha wave in adult males. *Korean J Nutr*. 2003;36(9):918-923.
- Lu K, Gray MA, Oliver C, et al. The acute effects of L-theanine in comparison with alprazolam on anticipatory anxiety in humans. *Hum Psychopharmacol*. 2004;19(7):457-465. doi:10.1002/hup.611
- Kimura K, Ozeki M, Juneja LR, Ohira H. L-Theanine reduces psychological and physiological stress responses. *Biol Psychol*. 2007;74(1):39-45. doi:10.1016/j.biopsycho.2006.06.006
- Nobre AC, Rao A, Owen GN. L-theanine, a natural constituent in tea, and its effect on mental state. *Asia Pac J Clin Nutr*. 2008;17(suppl 1):167-168.
- Kamei T, Toriumi Y, Kimura H, Ohno S, Kumano H, Kimura K. Decrease in serum cortisol during yoga exercise is correlated with alpha wave activation. *Percept Mot Skills*. 2000;90(3 Pt 1):1027-1032. doi:10.2466/pms.2000.90.3.1027
- White DJ, de Klerk S, Woods W, Gondalia S, Noonan C, Scholey AB. Anti-stress, behavioural and magnetoencephalography effects of an L-theanine-based nutrient drink: a randomised, double-blind, placebo-controlled, crossover trial. *Nutrients*. 2016;8(1):53. doi:10.3390/nu8010053
- Long SJ, Benton D. Effects of vitamin and mineral supplementation on stress, mild psychiatric symptoms, and mood in nonclinical samples: a meta-analysis. *Psychosom Med*. 2013;75(2):144-153. doi:10.1097/PSY.0b013e31827d5fbd
- Suni E. How sleep affects immunity. sleepfoundation.org. Updated November 19, 2020. Accessed September 2, 2021. <https://www.sleepfoundation.org/physical-health/how-sleep-affects-immunity>
- Hosseini-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc*. 2013;88(7):720-755. doi:10.1016/j.mayocp.2013.05.011
- Yamshchikov AV, Desai NS, Blumberg HM, Ziegler TR, Tangpricha V. Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. *Endocr Pract*. 2009;15(5):438-449. doi:10.4158/EP09101.0RR
- Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr*. 1998;68(suppl 2):447S-463S. doi:10.1093/ajcn/68.2.447S
- Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab*. 2007;51(4):301-323. doi:10.1159/000107673
- Marreiro DDN, Cruz KJC, Morais JBS, Beserra JB, Severo JS, de Oliveira ARS. Zinc and oxidative stress: current mechanisms. *Antioxidants (Basel)*. 2017;6(2):24. doi:10.3390/antiox6020024
- Carr AC, Maggini S. Vitamin C and immune function. *Nutrients*. 2017;9(11):1211. doi:10.3390/nu9111211
- Lewis ED, Meydani SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. *IUBMB Life*. 2019;71(4):487-494. doi:10.1002/iub.1976
- Suni E. Sleep guidelines during the COVID-19 pandemic. Sleep Foundation. April 7, 2021. Accessed August 8, 2021. <https://www.sleepfoundation.org/sleep-guidelines-covid-19-isolation>