

Vitamin D deficiency may increase risk for addiction to opioids and ultraviolet rays

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Vitamin D deficiency strongly exaggerates the craving for and effects of opioids, potentially increasing the risk for dependence and addiction, according to a new study led by researchers at Massachusetts General

Hospital (MGH). These findings, published in *Science Advances*, suggest that addressing the common problem of vitamin D deficiency with inexpensive supplements could play a part in combating the ongoing scourge of opioid addiction.

Earlier work by David E. Fisher, MD, Ph.D., director of the Mass General Cancer Center's Melanoma Program and director of MGH's Cutaneous Biology Research Center (CBRC), laid the foundation for the current study. In 2007, Fisher and his team found something unexpected: Exposure to ultraviolet (UV) rays (specifically the form called UVB), causes the skin to produce the hormone endorphin, which is chemically related to morphine, heroin and other opioids—in fact, all activate the same receptors in the brain. A subsequent study by Fisher found that UV exposure raises endorphin levels in mice, which then display behavior consistent with [opioid](#) addiction.

Endorphin is sometimes called a "feel good" hormone because it induces a sense of mild euphoria. Studies have suggested that some people develop urges to sunbathe and visit tanning salons that mirror the behaviors of opioid addicts. Fisher and his colleagues speculated that people may seek out UVB because they unknowingly crave the endorphin rush. But that suggests a major contradiction. "Why would we evolve to be behaviorally drawn towards the most common carcinogen that exists?" asked Fisher. After all, sun exposure is the primary cause of skin cancer, to say nothing of wrinkles and other skin damage.

Fisher believes that the only explanation for why humans and other animals seek out the sun is that exposure to UV radiation is necessary for production of vitamin D, which our bodies can't formulate on their own. Vitamin D promotes uptake of calcium, which is essential for building bone. As tribes of humans migrated north during prehistoric times, an evolutionary alteration might have been needed to compel them to step out of caves and into the sunshine on bitterly cold days. Otherwise, small

children would have died of prolonged vitamin D deficiency (the cause of rickets) and weak bones might have shattered when people ran from predators, leaving them vulnerable.

This theory led Fisher and colleagues to hypothesize that sun seeking is driven by vitamin D deficiency, with the goal of increasing synthesis of the hormone for survival, and that vitamin D deficiency might also make the body more sensitive to the effects of opioids, potentially contributing to addiction. "Our goal in this study was to understand the relationship between vitamin D signaling in the body and UV-seeking and opioid-seeking behaviors," says lead author Lajos V. Kemény, MD, Ph.D., a postdoctoral research fellow in Dermatology at MGH.

In the *Science Advances* paper, Fisher, Kemény and a multidisciplinary team from several institutions addressed the question from dual perspectives. In one arm of the study, they compared normal laboratory mice with mice that were deficient in vitamin D (either through special breeding or by removing vitamin D from their diets). "We found that modulating vitamin D levels changes multiple addictive behaviors to both UV and opioids," says Kemény. Importantly, when the mice were conditioned with modest doses of morphine, those deficient in vitamin D continued seeking out the drug, behavior that was less common among the normal mice. When morphine was withdrawn, the mice with low vitamin D levels were far more likely to develop withdrawal symptoms.

The study also found that morphine worked more effectively as a pain reliever in mice with vitamin D deficiency—that is, the opioid had an exaggerated response in these mice, which may be concerning if it's true in humans, too, says Fisher. After all, consider a surgery patient who receives morphine for pain control after the operation. If that patient is deficient in vitamin D, the euphoric effects of morphine could be exaggerated, says Fisher, "and that person is more likely to become addicted."

The lab data suggesting that vitamin D deficiency increases addictive behavior was supported by several accompanying analyses of human health records. One showed that patients with modestly low vitamin D levels were 50 percent more likely than others with normal levels to use opioids, while patients who had severe vitamin D deficiency were 90 percent more likely. Another analysis found that patients diagnosed with opioid use disorder (OUD) were more likely than others to be deficient in vitamin D.

Back in the lab, one of the study's other critical findings could have significant implications, says Fisher. "When we corrected vitamin D levels in the deficient mice, their opioid responses reversed and returned to normal," he says. In humans, vitamin D deficiency is widespread, but is safely and easily treated with low-cost dietary supplements, notes Fisher. While more research is needed, he believes that treating [vitamin D](#) deficiency may offer a new way to help reduce the risk for OUD and bolster existing treatments for the disorder. "Our results suggests that we may have an opportunity in the public health arena to influence the opioid epidemic," says Fisher.

More information: L.V. Kemény et al., "Vitamin D deficiency exacerbates UV/endorphin and opioid addiction," *Science Advances* (2021). advances.sciencemag.org/lookup...1126/sciadv.abe4577

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