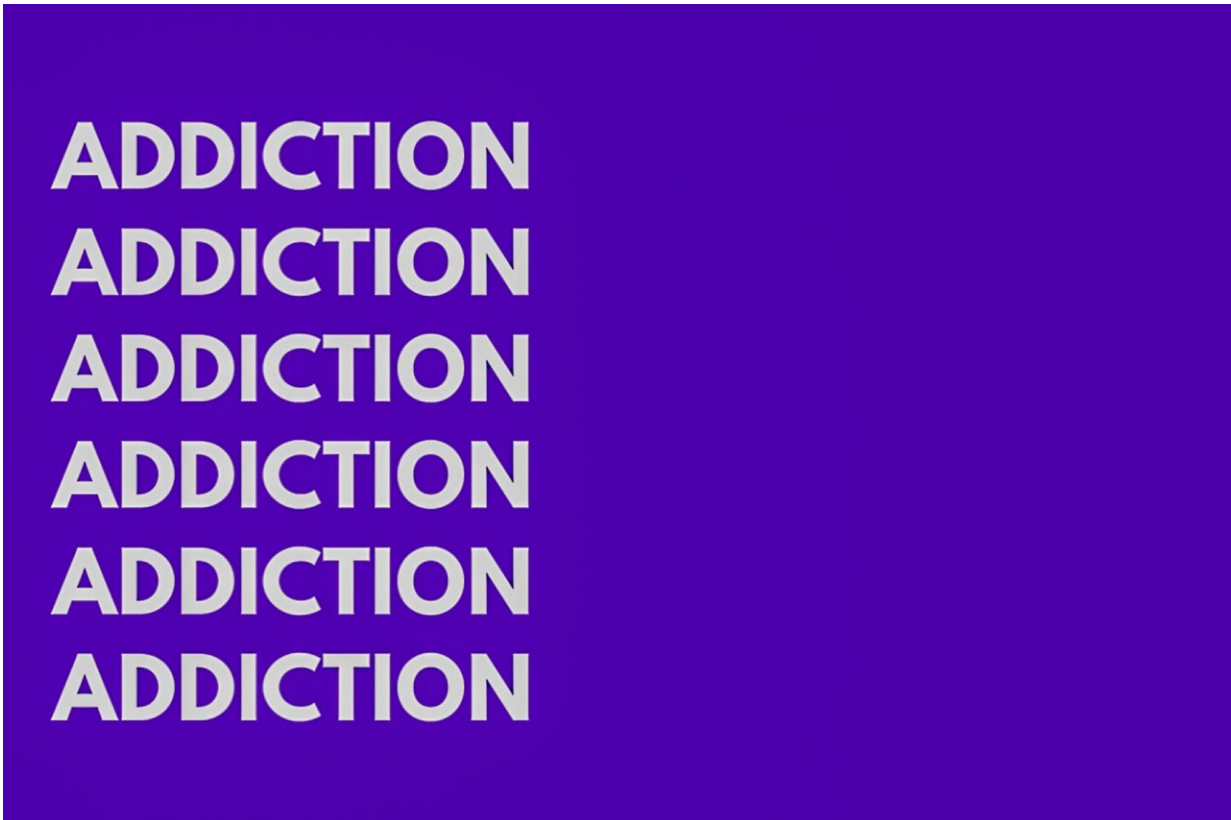


New research suggests estrogen and progesterone could play role in opioid addiction and relapse

July 17 2024, by Jessica Loweth and Daniel Manvich



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As opioid overdose deaths in the U.S. [rose dramatically](#) from 2014 to today, both [Philadelphia, Pennsylvania](#), and [Camden, New Jersey](#),

cemented reputations as hotspots of the crisis.

In Philadelphia, over 1,170 people [died of opioid overdoses in 2022](#), the last year for which complete data is available. More than 300 more [died just over the bridge in Camden County](#).

Research indicates that for many people with [opioid use disorder](#), misuse [starts with prescription painkillers](#).

As neuroscientists who study the [effects of addictive drugson the brain](#), we are working to better understand why some people are at greater risk for developing opioid dependence and addiction when taking prescribed opioids.

We are also striving to discover better treatments that can reduce drug cravings and prevent relapses in recovering users.

Sex differences and opioid addiction

There is some evidence that biological sex may play a role in both [opioid addiction](#) liability and relapse vulnerability.

For example, findings indicate that women are [more likely than men to be prescribed prescription opioids and to use them](#). They also [transition faster](#) from [initial use to more compulsive misuse](#).

Moreover, some studies have found that when trying to stay clean, women self-report [stronger cravings for opioids than men](#) and may experience [more severe withdrawal](#) symptoms. This suggests that women may also be at a greater risk for relapse.

What might underlie these [sex differences](#) in opioid misuse and relapse susceptibility? One possible factor is the difference between men and

women in the levels of the major sex hormones: testosterone, estrogen and progesterone.

Because estrogen and progesterone levels fluctuate naturally across the [menstrual cycle](#) in women—as well as during different stages of life such as pregnancy and menopause—we are examining whether opioid use and cravings vary as levels of these hormones change.

Hormones and drug cravings

To unravel the relationship between hormonal fluctuations and opioid rewards, many researchers have turned to rodent models. Rats in particular serve as an excellent model organism because their [reproductive cycle](#), referred to as the estrous cycle, is brief—lasting four to five days. Also, the pattern of fluctuations in rat estrogen and progesterone levels is [similar to that observed across the human menstrual cycle](#).

In [the Loweth lab](#), we have found that levels of cocaine cravings [vary across the estrous cycle](#). Specifically, cocaine cravings increase around the time of ovulation, after estrogen and progesterone levels have peaked.

In humans, [cocaine cravings are also stronger](#) around the time of ovulation, when estrogen levels are elevated.

However, much less is known about whether these hormonal fluctuations similarly affect opioid rewards or cravings.

Hormones and pain relief

To date, most of what we know regarding hormonal influences on opioid

drugs in humans comes from studies focused on their pain-relieving effects.

Although there are some conflicting reports, the data seem to suggest that opioid-induced pain relief is greatest in women during the phase of the menstrual cycle [leading up to ovulation](#). This is when estrogen levels are increasing and progesterone levels are low.

Opioid drugs relieve pain by binding to and activating proteins called opioid receptors at various nodes in the brain and spinal cord. The brain also makes its own natural version of opioids, called endogenous opioids. Research indicates that increasing estrogen levels can increase both [the number of opioid receptors](#) and the [levels of certain endogenous opioids](#) in various parts of the brain.

These changes could contribute to differences in opioid-induced [pain relief](#) across the menstrual cycle.

Hormones and opioid rewards and cravings

We and other researchers are working to determine whether estrogen and progesterone levels also influence the rewarding effects of prescription opioids, or cravings for these drugs.

In one set of studies, scientists trained rats to press a lever in order to receive intravenous infusions of heroin. The researchers found that the rats took less heroin [during a phase of the estrous cycle leading up to ovulation](#), when levels of estrogen and progesterone were elevated.

[Follow-up studies](#) later revealed that the rise in [estrogen](#), but not progesterone, [was responsible for this reduction in heroin intake](#).

Newer evidence suggests that this phenomenon may extend to

prescription opioids. In the [Manvich lab](#), we have discovered that the rewarding effects of the prescription opioid painkiller oxycodone are similarly reduced during cycle stages surrounding ovulation in which [estrogen and progesterone levels are rising or have just fallen](#) from peak levels.

Meanwhile, unpublished studies from the Loweth Lab found similar reductions in oxycodone craving across the rat estrous cycle. However, another recent study using slightly different methods [found no impact](#) of the estrous cycle on oxycodone cravings.

Such discrepancies highlight the need for further research to tease apart precisely how and when hormones affect the risk for former users of prescription opioids to experience a relapse.

This information could play an important role in how [health care providers](#) prescribe opioid medications—perhaps taking both biological sex and hormonal status into account—in order to minimize the risk of transitioning to prescription opioid misuse.

Ultimately, such efforts could reduce the incidence of opioid addiction and help combat the ongoing opioid crisis.

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