



NIH Researchers Discover Pain-Relieving Drug With Minimal Addictive Properties

Positive safety profile of novel drug compound is surprise for class of synthetic opioids shelved years ago.

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Researchers at the National Institutes of Health (NIH) have identified a novel, highly potent opioid that shows potential as a therapy for both pain and opioid use disorder. In a study published in [Nature](#), the team observed the new drug's effect in laboratory animals. They showed that it has high pain-relieving effects without causing respiratory depression, tolerance or other indicators of potential for addiction in humans.

"Opioid pain medications are essential for medical purposes, but can lead to addiction and overdose," said Nora D. Volkow, MD, director of NIH's National Institute on Drug Abuse (NIDA). "Developing a highly effective pain medication without these drawbacks would have enormous public health benefits."

The team investigated formulations of an understudied class of synthetic opioid compounds, known as nitazenes. Nitazenes selectively engage mu-opioid receptors, primary targets for opioid drugs in the brain and peripheral nervous system. However, nitazenes had been shelved in the 1950s due to their excessive potency. The scientific team revisited this class of compounds with a focus on harnessing their selectivity for the mu opioid receptor and engineering new nitazenes with a safer pharmacological profile.

"Our goal was to study the profile, or pharmacology, of these drugs," said Michael Michaelides, PhD, senior author and NIDA investigator. "We wanted to decrease the potency and create a potential therapeutic. What we discovered exceeded our expectations."

The team focused initially on a chemical formulation called FNZ that could be administered to rats and tagged with a radioisotope for positron emission tomography (PET). PET imaging enables tracking of the drug in real time throughout the rat brain. The team discovered that FNZ entered the brain only briefly, for approximately five to 10 minutes. Yet pain relief, known as analgesia, persisted for at least two hours. Knowing that nitazenes can have active metabolites, or by-products, the team investigated whether an FNZ metabolite might be responsible for the

prolonged effect. That investigation revealed DFNZ, another opioid dubbed a “superagonist” for its extremely high efficacy at the mu opioid receptor.

Whereas FNZ carries serious risks, including depressed breathing and high potential for addiction, DFNZ appears to sidestep these liabilities.

At preclinical therapeutic doses, DFNZ produced a moderate and sustained increase in brain oxygen rather than depressing respiration. Repeated doses of the drug did not result in tolerance, drug dependency, or meaningful withdrawal effects. Among 14 classic opioid withdrawal symptoms, the researchers only observed irritability, as measured by vocalization, when handling DFNZ-treated rats.

To test the drug’s rewarding effects, an important component of their addictive potential, the team studied its effects in rats who had been trained to press a lever for a dose of the pain-relieving drug. They found that animals readily self-administered DFNZ, indicating that it does produce some rewarding effect. However, when the drug was replaced with saline, animals stopped the drug-seeking behavior. The immediate behavior change is in contrast with what researchers see with other opioids such as heroin, morphine, and fentanyl. In those cases, animals typically persist in seeking the drug even after it is removed.

Further investigation revealed a likely neurochemical explanation. While DFNZ increases slow-acting dopamine release in the brain’s reward circuitry, it does not trigger the rapid dopamine bursts associated with the formation of strong drug-cue associations, the conditioned responses that drive craving and relapse in addiction.

“DFNZ has an unprecedented pharmacology for an opioid,” Michaelides said. “It is a potent and high-efficacy analgesic, but in certain contexts it resembles partial agonists, drugs that activate the receptor with low efficacy, which is what scientists think is needed for safety. Its capacity to be administered at therapeutic doses without producing respiratory depression is very important.”

The teams’ findings challenge the prevailing view that high-efficacy mu-opioid receptor drugs are unsuitable for development as safe analgesics. In fact, the authors of the paper maintain that DFNZ should be explored for use in treatment for opioid use disorder and may be preferable to current opioid agonist medications, which have an associated risk of causing respiratory depression.

The research team will pursue additional preclinical studies to support an application for regulatory approval to conduct studies of DFNZ in humans. They believe several patient populations may benefit from DFNZ, including those in surgical settings and with cancer-related or chronic pain who have a particularly high need for effective pain treatment.

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