

Opiates' side effects rooted in patients' genetics, study shows

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Genetics play a significant role in determining which patients will suffer the most from the disturbing side effects of opiates, commonly prescribed painkillers for severe to moderate pain, according to a new Stanford University School of Medicine study, which pinpoints nausea, slowed breathing and potential for addiction as heritable traits.

"One of the most hated [side effects](#) of these opiates, nausea, is strongly inherited," said Martin Angst, MD, professor of anesthesia and one of two [principal investigators](#) for the new study, which explores individual variations in the response to opiate use. The study will be published online June 20 in *Anesthesiology*. Genetics also play a likely role in determining which patients will suffer from itchiness and [sedation](#) associated with the use of these powerful medications, which include [morphine](#), [methadone](#) and [oxycodone](#).

"The study is a significant step forward in efforts to understand the basis of individual variability in response to opioids and to eventually personalize opioid treatment plans for patients," said Angst, director of the Stanford Human Pain Research Laboratory. "Our findings strongly encourage the use of downstream [molecular genetics](#) to identify patients who are more likely or less likely to benefit from these drugs — to help make decisions on how aggressive you want to be with treatment, how carefully you monitor patients and whether certain patients are suitable candidates for prolonged treatment."

Treatment with opiates, also known as narcotics, is tricky because of this

variability in drug response. Certain patients may require 10 times the amount of these [painkillers](#) to get the same level of pain relief as others. In fact, in some patients the occurrence of side effects may prevent the use of opioids for effectively alleviating pain. Side effects such as nausea or sedation can be debilitating to some, while nonexistent for others. Similarly, some patients can take medications for months with little addiction potential, while others are at risk within weeks.

Millions of U.S. patients are prescribed opiates for pain each year. A better understanding of the potential risk of side effects motivated the researchers to explore individual variation in pairs of identical and fraternal twins, Angst said. The study was prompted by past genetic studies in animals that have shown a strong genetic component in the response to opiates.

"We rely heavily on narcotics as the cornerstone medication for the relief of pain," said Angst. "Yet we don't know the answers to fundamental questions, such as why some people 'like' narcotics more than others — drug liking and disliking could be key in determining addiction potential."

Researchers recruited 121 twin pairs for the randomized, double-blinded and placebo-controlled study. Pain sensitivity and analgesic response were measured by applying a heat probe and by immersing a hand in ice-cold water, both before and during an infusion of the opiate alfentanil, a short-acting painkiller prescribed by anesthesiologists. The team also compared individual variations in levels of sedation, mental acuity, respiratory depression, nausea, itch, and drug-liking/disliking — a surrogate measure of addiction potential — between identical twins, non-identical twins and non-related subjects. This provided an estimate of the extent to which variations in responses to opiates are inherited. For example, the finding that identical twins are more similar in their responses to opiates than non-identical twins suggested inheritance plays

a significant role.

Heritability was found to account for 30 percent of the variability for respiratory depression, 59 percent of the variability for [nausea](#) and 36 percent for drug disliking. Additionally, up to 38 percent for itchiness, 32 percent for dizziness and 26 percent for drug-liking could be due to heritable factors. An earlier study published by the same researchers in the March issue of Pain reported that genetics accounted for 60 percent of the variability in the effectiveness of opiates in relieving pain.

"Since side effects are common among patients who use opioid medications, it will be beneficial to use such research to help at-risk [patients](#) avoid serious, life-threatening complications," said David Clark, MD, PhD, professor of anesthesia and the other principal investigator for the study.

Provided by Stanford University Medical Center

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