

Methadone's side effects, efficacy may be linked to genetic makeup

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Methadone can be lethal if it lingers too long in the body. New research at Washington University School of Medicine in St. Louis has identified genetic subtypes in people that govern methadone clearance, a discovery that could help prevent accidental overdoses. Credit: Robert Boston

Methadone—long used to treat pain and addiction to heroin and other opioid drugs—can be lethal itself if it lingers too long in the body. Although people are known to metabolize methadone differently, researchers have not completely understood how a person's genetic makeup influences how slowly or rapidly the drug is cleared.

Now, new research at Washington University School of Medicine in St. Louis has identified genetic subtypes in people that govern methadone clearance. If genetic testing is made available to patients prescribed the [drug](#), the new findings could help prevent some of the 5,000 deaths in the U.S. each year due to methadone overdoses.

"A person's [genetic makeup](#) influences how an enzyme in the liver metabolizes methadone," said principal investigator Evan D. Kharasch, MD, PhD, the Russell D. and Mary B. Shelden Professor of Anesthesiology and professor of biochemistry and molecular biophysics. "This explains why some people can have very high levels of methadone in their blood—high enough to trigger a potential overdose—even if they have received the same dose of the drug as others who are not affected the same way."

The study is available online in the journal *Anesthesiology*.

In the study, the researchers analyzed blood samples from healthy people to determine their genetic makeup. Then they gave the volunteers methadone to see how rapidly it cleared from their bodies. The researchers found that variations in a gene that influences methadone clearance in the liver made a big difference in how long the drug remained in the body and, consequently, how much pain relief—or risk of overdose—it provided.

Surprisingly, the researchers found that African-Americans in the study were more likely than Caucasians to have higher methadone concentrations in the blood despite being given equal dosages. They also showed that African-Americans more frequently had the gene variant linked to slower-than-normal clearance of methadone and less frequently had a genetic variant linked to faster methadone metabolism than Caucasians.

"We think that may explain why African-Americans and Caucasian patients typically clear methadone at different rates," he said.

Because of its varying metabolism, Kharasch said, methadone is a complicated drug to use.

For years, scientists assumed that an enzyme called cytochrome P4503A cleared methadone from the body. In fact, that's what the instructions packaged with the drug still say. However, in several studies from 2004-13, Kharasch and his colleagues found that another enzyme, called CYP2B6, is responsible for methadone clearance. Then they turned their attention to understanding how genetic variation in CYP2B6 affects methadone.

"There are two subtypes of the gene related to faster-than-normal or slower-than-normal clearance of methadone," said Kharasch, who also directs the new Center for Clinical Pharmacology, a joint effort of St. Louis College of Pharmacy and the School of Medicine to find better, safer and more effective ways to use prescription medications to improve health. "If people have one subtype of the gene, they are more likely to clear methadone rapidly, possibly resulting in inadequate pain control. But people with a different subtype of the gene seem to clear the drug more slowly, potentially contributing to the risk of overdose."

In addition, the team found that clearance of the oral form of methadone was more likely to be affected by a person's genetic makeup than clearance of the intravenous form of the drug. That's important because it's more likely the oral form would be prescribed by primary care providers who may not be as familiar with the difficulties involved in using [methadone](#) to treat pain as anesthesiologists and other specialists in pain management.

More information: Evan D. Kharasch et al. Methadone

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