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Combining epilepsy drug, morphine can result in less pain, lower opioid doses

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Adding a common epilepsy drug to a morphine regimen can result in better pain control with fewer side effects. Moreover, the combination can reduce the dosage of the opioid needed to be effective, according to a team of pain researchers at Indiana University.

The result could bring significant relief to many patients with neuropathic pain, a difficult-to-treat condition often felt in the arms and legs and associated with nerve tissue damage.

"There is a huge unmet need for better treatments for neuropathic pain," said Fletcher A. White, Ph.D., the Vergil K. Stoelting Professor of Anesthesia at the Indiana University School of Medicine.

In laboratory tests using rodents, White and his colleagues found that while morphine lost its pain-relieving effectiveness three weeks after nerve injury, a combination therapy of morphine and carbamazepine—used to prevent epileptic seizures—could effectively reverse this loss of drug action. Their findings were reported in the journal *PLOS One*.

Although morphine and related opioid drugs are effective in treating pain, they can result in dependence and produce side effects including respiratory depression, nausea, constipation and other problems. In addition, such drugs can, paradoxically, actually cause pain, a condition called opioid-induced hyperalgesia.

"People immediately think, 'Oh, it's tolerance, the patient needs more of the drug for pain control,'" Dr. White said.

In fact, research indicates that the pain of hyperalgesia occurs because the morphine latches on not only to cellular targets that reduce pain sensation but to other "non-opioid" targets that result in activation of pain-sensing neurons. Dr. White and his colleagues had previously identified a key cellular factor—known to be a specific voltage-gated sodium ion channel—involved in that non-opioid process of pain nerve stimulation. Meanwhile another IU School of Medicine researcher, Theodore Cummins, Ph.D., professor of pharmacology and toxicology, had previously determined that carbamazepine alone has the opposite effect on the same ion channel.

Combining the two drugs could prevent the escalating doses of opioids that are sometimes prescribed to provide pain relief in the clinic.

"We know that opioids have benefits," Dr. White said. "If we can diminish the off-target effects, that's good. If we can diminish the opioid dosages required for pain relief, then you've really got something."

Because both drugs are approved for use by the Food and Drug Administration, physicians have tested the combination with patients, resulting in anecdotal reports of significantly improved pain management, Dr. White said. More formally, Dr. White and physician-researchers have begun testing the combination of morphine and a close relative of carbamazepine with patients in a small clinical trial at the Indiana University Melvin and Bren Simon Cancer Center.

Provided by Indiana University

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