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A path to lower-risk painkillers

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For patients managing cancer and other chronic health issues, painkillers such as morphine and Vicodin are often essential for pain relief. The body's natural tendency to develop tolerance to these medications, however, often requires patients to take higher doses – increasing risks of harmful side effects and dependency.

Now, new research from the University of Michigan Health System and a major pharmaceutical company has identified a novel approach to moderate and severe pain therapy that paves the way for lower dosage painkillers. The findings appear in *Proceedings of the National Academy of Sciences* of the United States of America.

Drugs such as hydrocodone (the main ingredient of Vicodin) and oxycodone (Oxycontin) are often the best options for the treatment of moderate to severe pain for patients facing medical conditions ranging from a wisdom tooth extraction to cancer. The drugs bind to specific molecules (opioid receptors) on nerve cells in the brain and spinal cord to prevent the feeling of pain.

"We have for the first time discovered compounds that bind to an alternative site on the nerve opioid receptors and that have significant potential to enhance the drug's positive impact without increasing negative side effects," says co-author John Traynor, Ph.D., professor of pharmacology at the U-M Medical School.

"We are still in the very early stages of this research with a long way to go, but we believe identifying these compounds is a key step in

revolutionizing the treatment of pain. This opens the door to developing pain relief medications that require lower doses to be effective, helping address the serious issues of tolerance and dependence that we see with conventional pain therapy."

Conventional drug treatments for pain work by targeting the so-called orthosteric site of the opioid receptor that provides pain relief. Targeting this site, however, is a double-edged sword because it is also responsible for all of the drug's unwanted side effects, such as constipation and respiratory depression. Tolerance also limits chronic use of the drugs because higher doses are required to maintain the same effect.

Using cell systems and mouse brain membranes, researchers have identified compounds that bind to a physically distinct and previously unknown "allosteric" site on the opioid receptor- a site that fine-tunes the activity of the receptor. Not only do these compounds act at a location that hasn't been studied as a drug target before but they bind to the receptor in a new way to enhance the actions of morphine – which means lower doses can have the same impact.

"The newly-discovered compounds bind to the same receptor as morphine but appear to act at a separate novel site on the receptor and therefore can produce different effects. What's particularly exciting is that these compounds could potentially work with the body's own natural painkillers to manage pain," Traynor says.

"We know that conventional strong pain medications ultimately increase the risk of withdrawal symptoms and addiction, which is an especially serious issue with the current prescription drug abuse epidemic in our country. The implications of this work, if it translates to animal studies and then to humans, are highly significant to this area of study."

More information: "Discovery of Positive Allosteric Modulators and

Silent Allosteric Modulators of the Mu Opioid Receptor," *Proceedings of the National Academy of Sciences* : www.pnas.org/cgi/doi/10.1073/pnas.1300393110