Insights on brain-spinal communication in opioid withdrawal lead to a clinical trial

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Tuan Trang (left) and Lori Montgomery discuss the clinical trial using an anti-gout medication to address the severe symptoms of of opioid withdrawal. Credit: Riley Brandt, University of Calgary

A deeper understanding of the communication inside the body when

someone is going through opioid withdrawal has led to a new clinical trial at the University of Calgary.

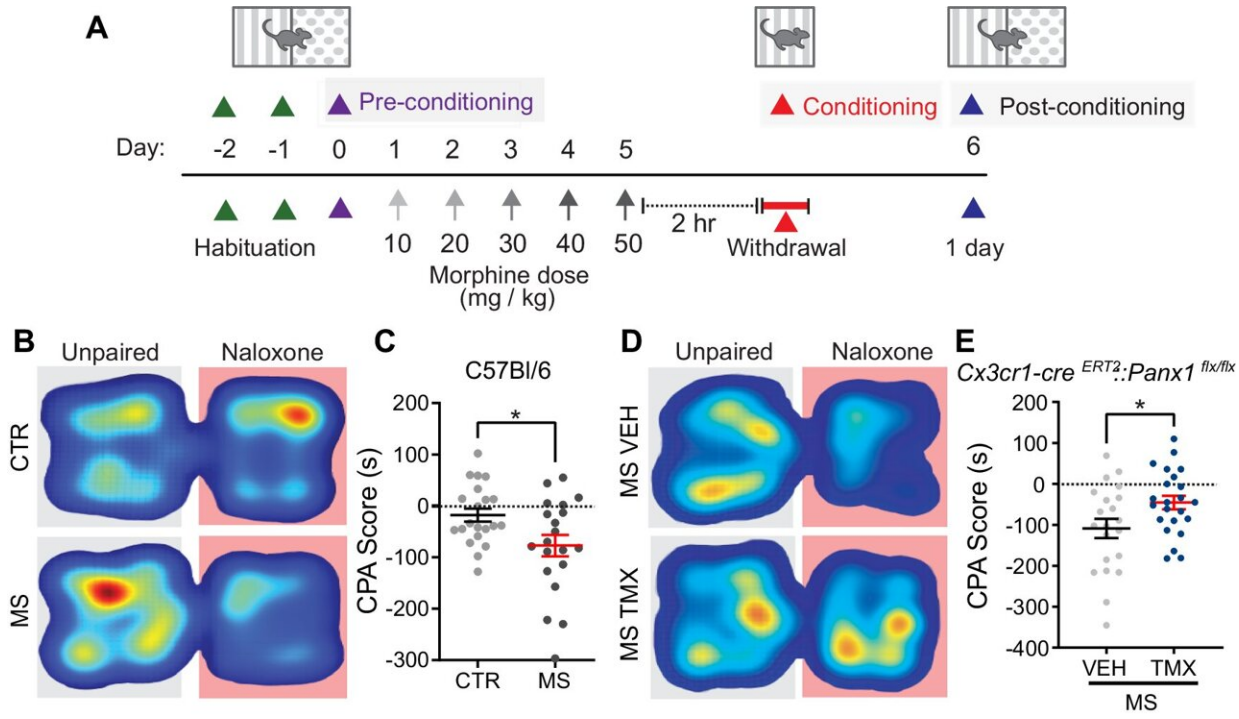
"I don't think I've had a day in the clinic in the last five years where I haven't had a patient tell me they want to reduce the opioids they are taking," says Dr. Lori Montgomery, MD, pain clinician and clinical lead for an opioid tapering study. "The problem is there are limited options to support them, and the withdrawal symptoms can be crippling."

Montgomery, an associate professor at the Cumming School of Medicine (CSM), is recruiting people for a clinical trial using a safe, well-tolerated drug for gout, probenecid, to help with the disabling symptoms of opioid withdrawal.

"One of the first symptoms is really severe pain. It's very uncomfortable, and it's one of the biggest reasons people remain on opioids long-term even if the opioids are no longer effective in reducing their chronic pain," says Montgomery.

The clinical trial Montgomery is leading is based on research done by Dr. Tuan Trang, Ph.D., a professor in the Faculty of Veterinary Medicine. His lab has been studying how opioids affect key pain centers in the nervous system. In 2017, his research team made a breakthrough discovery that probenecid effectively reduces opioid withdrawal in rodents. Recently, they unraveled how this medication disrupts the abnormal brain-spinal cord communication that occurs during opioid withdrawal.

"The area of the brain that is sending the signal regulates the autonomic system, our fight-or-flight response," says Trang, principal investigator on the new study recently published in *Nature Communications*. "During withdrawal, that center in the brain is hyperactive, contributing to the body's reaction during withdrawal."



Deletion of microglial Panx1 alleviates morphine withdrawal induced conditioned place aversion. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-50657-7

Trang says understanding the underlying neurobiology is important for developing a potential treatment for opioid withdrawal in people.

For the pilot 12-week randomized control trial, Trang and Montgomery, both members of the Hotchkiss Brain Institute at the CSM, are recruiting people aged 18 and over who have a goal to taper or stop the opioids they are taking.

"Probenecid has not been tested for opioid withdrawal before, but we know it is a safe and well tolerated drug. Headache and nausea are the most common side effects, which can be addressed," says Montgomery.

"We start with doses that are lower than what has been used for gout. If the person is tolerating the drug well, we start to taper the opioids they are taking and measure whether they experience withdrawal."

Montgomery says anyone can become physically dependent on opioids within a couple of weeks and they need to taper to stop use of the drug. She adds Canada is the highest prescriber of opioids in the world.

"We have learned so much in the last 15-20 years—for many people with chronic pain, the risks outweigh the benefits, there are lots of consequences, and the benefits long-term aren't there," says Montgomery.

Trang says being part of translating scientific discovery to a potential treatment for a complex societal issue is encouraging and demonstrates the power of transdisciplinary collaboration. He says that the work is made possible because of exceptionally talented team members and collaborators, notably, the co-lead authors of the research study, Drs. Charlie Kwok, Ph.D., Erika Harding, Ph.D., and Nicole Burma, MD, Ph.D.

More information: Charlie H. T. Kwok et al, Pannexin-1 channel inhibition alleviates opioid withdrawal in rodents by modulating locus coeruleus to spinal cord circuitry, *Nature Communications* (2024). DOI: 10.1038/s41467-024-50657-7

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