

# New compound outperforms pain drug by indirectly targeting calcium channels

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A compound—one of 27 million screened in a library of potential new drugs—reversed four types of chronic pain in animal studies, according to new research led by NYU College of Dentistry's Pain Research Center and [published in the \*Proceedings of the National Academy of Sciences\*](#) (

[PNAS](#)).

The small molecule, which binds to an inner region of a calcium channel to indirectly regulate it, outperformed gabapentin without troublesome side effects, providing a promising candidate for treating [pain](#).

Calcium channels play a central role in pain signaling, in part through the release of neurotransmitters such as glutamate and GABA— "the currency of the pain signal," according to Rajesh Khanna, director of the NYU Pain Research Center and professor of molecular pathobiology at NYU Dentistry. The Cav2.2 (or N-type) calcium channel is the target for three clinically available drugs, including gabapentin (sold under [brand names](#) including Neurontin) and pregabalin (Lyrica), which are widely used to treat nerve pain and epilepsy.

Gabapentin mitigates pain by binding to the outside of the Cav2.2 calcium channel, affecting the channel's activity. However, like many pain medications, gabapentin use often comes with side effects.

"Developing effective pain management with minimal side effects is crucial, but creating new therapies has been challenging," said Khanna, the senior author of the *PNAS* study. "Rather than directly going after known targets for pain relief, our lab is focused on indirectly targeting proteins that are involved in pain."

## Inside the channel

Khanna has long been interested in a protein called CRMP2, a key regulator of the Cav2.2 calcium channel that binds to the channel from the inside. He and his colleagues [previously discovered a peptide](#) (a small region of amino acids) derived from CRMP2 that could uncouple CRMP2 from the calcium channel.

When this peptide—dubbed the calcium channel-binding domain 3, or CBD3—was delivered to cells, it acted as a decoy, blocking CRMP2 from binding to the inside of the calcium channel. This resulted in less calcium entering the calcium channel and less neurotransmitter release, which translated to less pain in animal studies.

Peptides are difficult to synthesize as drugs because they are short-acting and easily degrade in the stomach, so the researchers sought to create a small molecule drug based on CBD3. Starting with the 15 amino acids that make up the CBD3 peptide, they honed in on two amino acids that studies showed were responsible for inhibiting calcium influx and mitigating pain.

"At that point, we realized that these two amino acids could be the [building blocks](#) for designing a small molecule," said Khanna.

## **From 27 million to one**

In collaboration with colleagues at the University of Pittsburgh, the researchers ran a computer simulation that screened a library of 27 million compounds to look for a small molecule that would "match" the CBD3 amino acids.

The simulation narrowed the library down to 77 compounds, which the researchers experimentally tested to see if they lessened the amount of calcium influx. This further pared the pool down to nine compounds, which were assessed using electrophysiology to measure decreases in electrical currents through the [calcium channels](#).

One compound, which the researchers named CBD3063, emerged as the most promising candidate for treating pain. Biochemical tests revealed that CBD3063 disrupted the interaction between the CaV2.2 calcium channel and CRMP2 protein, reduced calcium entering the channel, and

lessened the release of neurotransmitters.

"Many scientists have screened the same library of compounds, but have been trying to block the calcium channel from the outside. Our target, these two [amino acids](#) from CRMP2, is on the inside of the cell, and this indirect approach may be the key to our success," said Khanna.

## **Four labs, four types of pain**

Khanna's lab then tested CBD3063 with mouse models for pain related to injury. The compound was effective in alleviating pain in both male and female mice—and notably, in a head-to-head test with the drug gabapentin, the researchers needed to use far less CBD3063 (1 to 10 mg) than gabapentin (30 mg) to reduce pain.

To explore whether CBD3063 helped with different types of chronic pain, Khanna partnered with researchers at Virginia Commonwealth University, Michigan State University, and Rutgers University. Collaborators ran similar studies administering CBD3063 to treat animal models of chemotherapy-induced neuropathy, inflammatory pain, and trigeminal nerve pain—all successfully reversing pain, similar to gabapentin.

But unlike gabapentin, the use of CBD3063 did not come with side effects, including sedation, changes to cognition such as memory and learning, or changes to heart rate and breathing.

## **What's next**

The researchers are continuing to study CBD3063, refining its [chemical composition](#) and running additional tests to study the compound's safety and assess if tolerance develops.

Long-term, they hope to bring a CBD3063-derived drug to [clinical trials](#) in an effort to offer new options for safe and effective [pain relief](#).

"Identifying this first-in-class small molecule has been the culmination of more than 15 years of research. Though our research journey continues, we aspire to present a superior successor to gabapentin for the effective management of chronic pain," said Khanna.

**More information:** Khanna et al, A peptidomimetic modulator of the CaV2.2 N-type calcium channel for chronic pain, *Proceedings of the National Academy of Sciences* (2023). [DOI: 10.1073/pnas.2305215120](https://doi.org/10.1073/pnas.2305215120). [doi.org/10.1073/pnas.2305215120](https://doi.org/10.1073/pnas.2305215120)

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