As opioids continue to cause significant safety and cost concerns, drug developers have gained traction experimenting with new entities that target non-opioid pain neuropathways in the brain, which could potentially deliver safer alternatives for pain relief.

FAST FOCUS

An estimated 100 million Americans suffer from chronic pain, and as the devastating impacts of the opioid epidemic continue to reverberate, there remains a significant and unmet need for non-opioid pain medications that can safely and effectively manage pain, without presenting the risks posed by opioids.

One trending model drug developers are employing to meet this need is the creation of new medications that reduce pain by targeting different neurochemical pain pathways in the brain, going beyond traditional opioid pathways.

A BRIEF HISTORY OF OPIOID RECEPTORS

Opioid medications produce their analgesic effects by binding to special opioid receptors in the brain, triggering nerve cells to reduce pain messages sent to the brain. However, stimulating these opioid receptors is also what leads to adverse drug effects, such as respiratory depression, nausea, and importantly, the euphoric high that can eventually contribute to dependence, misuse, and abuse.

Despite the risks involved, opioids have remained popular because this mechanism of action is incredibly effective in providing pain relief. But as science continues to progress, researchers have increasingly been targeting other neuropathways in the brain that play active roles in the transmission of pain.

TRACKING A NEW PATH

The FDA recently granted Fast Track designation to tanezumab, a non-opioid biologic currently in Phase 3 development for the treatment of chronic low-back pain and osteoarthritis. Tanezumab is a special antibody that targets, binds to, and inhibits nerve growth factor (NGF). NGF is an important mediator of pain initiation and maintenance, and researchers believe pharmacotherapies that target this pathway could show significant promise in the treatment of pain. Clinical trials for tanezumab are expected to produce results in 2018, and tanezumab’s Fast Track designation increases collaboration between drug developers and the FDA, which could improve the drug’s chances of FDA approval as the FDA would offer more insight and feedback.

To qualify for Fast Track status, drugs must treat unmet medical needs. The FDA’s decision to Fast Track tanezumab indicates the agency’s belief that drugs like tanezumab, which target non-opioid receptors involved in the sensation of pain, have the potential to effectively treat pain with fewer risks than currently available opioid medications.

This potentially opens the door to more investment in drugs that target non-opioid pain neuropathways, which could lead to a wave of new pain medications.

BRANCHING OUT OF THE OPIOID BUBBLE

The field of neuroscience is incredibly complex, but researchers have been studying a wide range of other neuropathways that help transmit pain. In some cases, they have developed compounds that can affect those neuropathways to impact pain, and an exploration of these alternatives may serve to benefit patients in the near future, if these products prove safe and effective. (Please see the next page for an overview of current research being undertaken in neuropathways, and associated molecules in development.)
TRP Channels
TRP channels mediate a variety of sensations, including pain, and inhibiting these channels can decrease sensitivity to a variety of stimuli. There are many subclasses of TRP channels, and of those subsets, several play a part in transmitting pain.

Sigma-1 Receptors
Sigma-1 receptors are located in areas of the central nervous system that are key for pain control, and preclinical evidence supports the role of sigma-1 antagonists for the treatment of pain.

SSTR4 Receptors
SSTR4 receptors play a critical role in the regulation of pain by controlling several other pain receptors, and so it is believed an SSTR4 agonist could prove useful for the treatment of pain and inflammation.

CCR2 Receptors
CCR2 receptors are central to the development of pain associated with osteoarthritis, and so researchers believe inhibiting these receptors could reduce osteoarthritis pain.

Nav1.7 Channels
Nav1.7 is a sodium ion channel present at the endings of pain-sensing nerves. Loss of Nav1.7 is linked to an inability to experience pain, and local anesthetics have been known to non-selectively block Nav1.7.

NON-OPIOID PAIN MANAGEMENT RESEARCH
These drugs are just a few examples of many products in development. More research is needed in this field, especially as it is not yet fully understood what impact these medications may have on other systems in the body.

Preclinical

Phase 1 Trials
- CNTX-6970 is a CCR2 antagonist that inhibits CCR2 receptors from releasing and stimulating pain fibers. CNTX-6970 successfully completed Phase 1 clinical trials for chronic painful inflammation conditions, such as osteoarthritis.

Phase 2 Trials
- TV-45070 is a small molecule inhibitor of sodium channel Nav1.7 and other sodium channels, including those expressed in pain-sensing within the peripheral nervous system. This drug is a topical ointment intended to be used over painful joints and for neuropathic pain. After completing Phase 2B clinical trials, TV-45070 did not meet primary endpoints in patients with shingles pain, but developers of TV-45070 are still exploring other pain indications.

Phase 3 Trials
- CNTX-4975 targets TRPV1 receptors to inactivate local pain fibers transmitting signals to the brain. The drug completed Phase 2B clinical trials and met primary endpoints for osteoarthritis knee pain, with pain relief lasting six months following a single injection. The drug clears the body within 24 hours and will start Phase 3 clinical trials soon.

GDC-0310 (RG6029) is a selective, reversible, orally bioavailable small-molecule sodium channel blocker that is selective for Nav1.7. This drug completed Phase 1 clinical trials and is expected to initiate Phase 2 clinical trials.

CNTX-0290 is a first-in-class SSTR4 agonist which researchers believe can target a broad range of chronic pain types. The drug was well tolerated in Phase 1 clinical trials and will soon go into Phase 2 trials.

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S1A (MR309/E-S286G) is a highly selective sigma 1 antagonist that is being studied for use in the management of neuropathic pain. Phase 2 clinical trials are currently evaluating the drug's efficacy profile in the treatment of peripheral neuropathy and post-operative pain.

Preclinical

Phase 1 Trials
- Compound 16-8 is as dual inhibitor that targets and inhibits TRPV4, which is involved in pain and inflammation, and TRPA1, which is known to function as a chemical sensor of noxious and irritant signaling. This compound has yet to enter clinical trials.

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