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## The Heated Quest for Opioid Alternatives

Drugmakers are pursuing a number of new drugs that show less risk of abuse

BY BRIAN GORMLEY

RISING ABUSE of prescription painkillers is intensifying a search for alternatives to addictive opioids.

Overdoses of prescription opioids kill about 46 Americans a day, according to the Centers for Disease Control and Prevention. Despite that toll, opioids remain in widespread use because they are powerful painkillers, and many attempts to develop new therapies have failed.

But drugmakers are exploring a growing number of potential alternatives and are conducting clinical trials of several painkillers designed to have little or no risk of abuse or addiction. "Pain drugs are going to get better," says Neil Singla, chief scientific officer at Lotus Clinical Research LLC, a company that conducts clinical trials and specializes in pain studies. "We've got enough darts out there that someone's going to hit the bull's-eye."

The search for new treatments is a race not only against the tide of opioid abuse but also against the aging of America. With the population developing more back problems, joint diseases and other age-related illness, pain is ubiquitous. More than 25 million Americans suffer from daily pain, according to the National Institutes of Health.

Clinicians also will need better options as more people survive cancer and other diseases and suffer the painful side effects of treatment, says Peter Staats, chief medical officer of National Spine & Pain Centers, a pain-management practice based in Rockville, Md. "We desperately need alternatives" for managing pain, Dr. Staats says.

### New tactics

Opioids, which activate specific receptors in the brain, spinal cord and elsewhere, can cause euphoria that leads to addiction. They can also cause problems like nausea, vomiting and breathing troubles.

Drugmakers hope to sidestep these effects by targeting new molecules and avoiding opioid receptors. One new target is nerve growth factor.

In fetuses and infants, this protein, as its name suggests, promotes nerve growth. But when the nervous system matures, NGF's role is to process pain signals, says Ken Verburg, who heads Pfizer Inc.'s effort with partner Eli Lilly & Co. to develop a drug that binds to nerve growth factor to prevent it from activating pain-signaling neurons.

That medicine, tanezumab, has shown promise in several conditions. For example, a study published in the journal PAIN found that in chronic low-back pain, tanezumab provided significantly greater improvement in pain and physical func-



tion compared with a placebo or naproxen, a type of pain reliever known as an NSAID, or nonsteroidal anti-inflammatory drug.

Phase 3 studies are continuing in osteoarthritis, chronic low-back pain and cancer pain, and results in osteoarthritis are expected in the second half of this year, Dr. Verburg says.

### New injections

Tanezumab is one of several agents that could offer a new way to manage osteoarthritis—in which cartilage degenerates and changes occur to the underlying bone—and so make it less likely that patients will need opioids for the pain.

One new option is Zilretta, which is injected into the knee and is designed to provide longer-lasting relief than generic corticosteroid shots used for short-term pain treatment. Zilretta, which received Food and Drug Administration approval in October, treats pain as a corticosteroid is gradually released from tiny globes known as microspheres.

Zilretta developer Flexion Therapeutics Inc., based in Burlington, Mass., studied the drug in Phase 3 clinical trials comparing Zilretta to a placebo and an immediate-release corticosteroid. These trials, published in the Journal of Bone and Joint Surgery, found that the drug met its primary goal of providing significant pain relief compared with a placebo over 12 weeks.

Side effects of corticosteroids that could occur with Zilretta treatment include infection in the injected knee, according to the company.

An experimental drug from Centrexion Therapeutics Corp., a Bos-

### Options Needed

From 1999 to 2016, more than 200,000 people died in the U.S. from overdoses related to prescription opioids.  
Statistics for 2016 alone:

**42,249**

Deaths from opioid-related drug overdoses

**46**

Daily deaths from overdoses involving prescription opioids

**17,087**

Deaths attributed to overdosing on commonly prescribed opioids

**2.1 million**

People had an opioid-use disorder

**11.5 million**

People misused prescription opioids

Sources: Department of Health and Human Services; Centers for Disease Control and Prevention  
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ton-based startup, is also injected into the knee joint. The product inactivates the ends of pain fibers in nerves for months until they eventually grow back, Centrexion says.

The drug doesn't affect other fibers in nerves, so sensations like touch and pressure remain intact, says Kerrie Brady, Centrexion's chief business officer. "You don't have a numb knee," she says, "you just have a knee that doesn't hurt."

In Phase 2 clinical trials, pain reduction began within days and continued for six months, Centrexion says. There were also reductions in

knee stiffness and improvement in joint function, according to Centrexion, which is now testing the treatment in Phase 3 studies.

"It's a promising treatment," says Marc Hochberg, professor of medicine and epidemiology and public health at the University of Maryland School of Medicine, who isn't involved in Centrexion trials. "Based on the data we currently have available, it showed promise which hopefully will be replicated in Phase 3 clinical trials."

### After surgery

Other localized treatments aim to reduce opioid use after surgery. Pacira Pharmaceuticals Inc.'s Exparel secured U.S. regulatory approval in 2011 and can be used to treat the pain of surgical wounds. The product slowly releases the local anesthetic bupivacaine to control pain for two to three days after surgery, according to Pacira, which says it saw a 78% reduction in overall opioid consumption in studies of patients receiving Exparel compared with conventional bupivacaine that limits pain for a few hours.

Jonathan Friedstat, an acute-burn and reconstructive plastic surgeon at Massachusetts General Hospital, has used Exparel in patients who need to have a thin layer of skin shaved from one part of the body and grafted onto another part that has been burned. Skin harvesting often causes more pain than the burn itself, according to Dr. Friedstat, who has used Exparel along with conventional bupivacaine to treat these wounds during surgery.

Three-quarters to 90% of patients have had a good response to Exparel

in his experience, Dr. Friedstat says, adding that these people need far less opioid therapy after surgery. "When it works, they need very little narcotic," he says. In April, Parsippany, N.J.-based Pacira gained a new approval from the FDA allowing Exparel to also be used as a nerve block to curb pain in the shoulder region after shoulder surgeries.

Another company, Heron Therapeutics Inc., says it recently saw reduced pain and opioid use in Phase 3 trials of a medicine that combines a long-acting bupivacaine with an anti-inflammatory agent.

Bupivacaine is sensitive to drops in pH caused by inflammation in the surgical site, according to Heron Chief Executive Barry Quart. Adding the anti-inflammatory agent meloxicam raises the pH to normal levels that existed before surgery. That allows more bupivacaine to enter nerves and stop pain signals from being relayed to the brain, Dr. Quart says.

In Phase 3 trials, bunion-surgery patients receiving the drug had pain reductions of 27% and 18%, respectively, compared with a placebo and conventional bupivacaine, according to Heron. And over 72 hours after surgery, opioid use was 37% less and 25% less, respectively, in patients getting the drug compared with those getting a placebo or conventional bupivacaine, according to San Diego-based Heron.

Heron, which also saw good results in Phase 3 studies of hernia-repair patients, plans to seek U.S. regulatory approval for postoperative pain in the second half of this year, Dr. Quart says.

### A better opioid?

Another approach to easing opioid addiction is to build a better opioid, designed not to produce euphoria. Commonly prescribed opioids induce euphoria—and a desire to continue using the drug—by triggering a spike in the level of the chemical messenger dopamine in the brain's reward center, says Stephen Doberstein, chief research and development officer of Nektar Therapeutics.

San Francisco-based Nektar says it has engineered a new opioid that enters the brain slowly to reduce the release of dopamine. A study published in the journal Pain Medicine of healthy, adult recreational drug users not physically dependent on opioids found Nektar's drug was less likable to them than the opioid oxycodone. The company says it plans to file soon for FDA approval.

"We've dramatically blunted likability," Dr. Doberstein says. "It doesn't appear to cause this euphoric effect that old-fashioned drugs do."

*Mr. Gormley is a Wall Street Journal reporter in Boston. Email [brian.gormley@wsj.com](mailto:brian.gormley@wsj.com).*

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