

# Pain and Progress

Is it possible to make a nonaddictive opioid painkiller?

By Kerry Grens | February 1, 2014

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**F**or thousands of years, humans have turned to opioids to relieve their pain. Morphine and its cousin compounds work so magnificently to blunt feelings of pain that, in 4,000 years of use, we have found nothing to top them. As the famous 17th-century physician Thomas Sydenham put it, “Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.” Today, physicians write more than 200 million prescriptions for opioid painkillers in the U.S. each year.

But it’s well known that opioids have a dark side. As good as the drugs are at stopping pain, they also arouse a hardwired reward network in the human brain, eliciting strong feelings of euphoria that can drive craving, dependency, and addiction. As long as there has been opium use, there have been opium addicts.

In December 1995, the US Food and Drug Administration (FDA) approved OxyContin, a delayed-release formulation of oxycodone, a semisynthetic opioid that has been used as an analgesic for almost a century. The idea was that extending the medicine’s absorption time would prevent abuse, because users wouldn’t get an immediate high from swallowing a tablet. The drug worked well—curbing pain as effectively as the original oxycodone—and the number of prescriptions skyrocketed. Soon enough, however, people figured out that crushing the pills and snorting or injecting the drug could generate an epic high, and by 2000, Purdue Pharma, the maker of OxyContin, was receiving reports that its product was being abused.

“It was all hands on deck” to solve the problem, says Jennifer Giordano, the director of analytics at Purdue. But a decade later, prescription opioid abuse and addiction had reached epidemic proportions. In 2010, more than

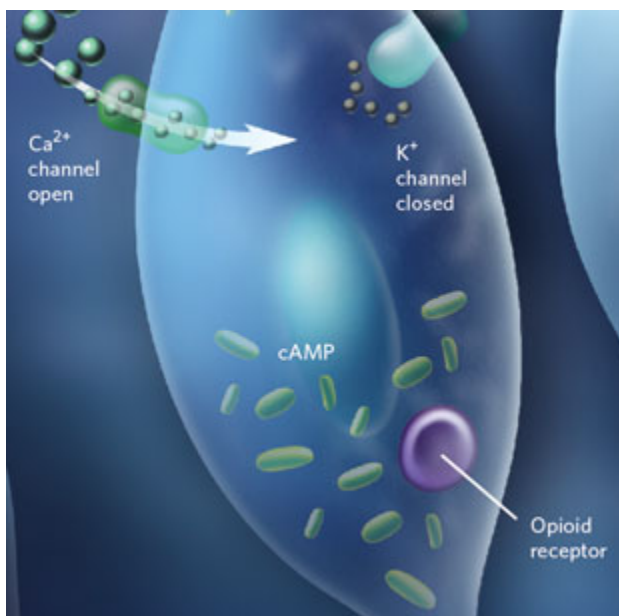
16,000 people in the U.S. died of an opioid painkiller overdose; in 2009, the drugs sent 475,000 people to the emergency room.

"The numbers are sobering," says Douglas Throckmorton, the deputy director of regulatory programs in the FDA's Center for Drug Evaluation and Research. "They're the kinds of numbers that call on everybody to do all the things they possibly can."

The question is what to do. Restricting the use of opioids is not likely to happen. The drugs are the only painkillers that work for many people, and an astounding number of patients suffer from pain. "It's quite a quandary, because we have 100 million people in this country who are in pain, and a lot of them need [opioid medications]," says Dave Thomas, the deputy director of the Division of Clinical Neuroscience and Behavioral Research at the National Institute on Drug Abuse. "We're caught between trying to medicate people in pain and trying not to exacerbate the epidemic."

So, scientists are getting creative, tweaking opioids' mechanisms of action in the body and brain, combining opioids with other compounds that can limit the opioid high while retaining the drugs' pain-killing power, and designing new abuse-deterrent technologies that addicts might not be able to crack. In all cases, the end goal is the same: develop an effective, nonaddictive painkiller.

## Hurts so good



**ONE MECHANISM OF OPIOID ACTION:** When an opioid binds to an opioid receptor in the membrane of a neuron, calcium channels close, blocking positively charged calcium ions from entering the cell. In addition, cAMP levels decrease and potassium channels open, allowing positive potassium ions to exit the cell. These events hyperpolarize the cell, increasing the charge difference between the cell's interior and the extracellular environment and making the neuron less likely to fire an action potential.

**See full infographic:** [JPG](#) | [PDF](#) © THOM GRAVES Opioids bind to the receptors that modulate pain perception, hunger, thirst, mood, and other processes. Whether produced naturally in the brain or a poppy pod, or synthetically in the laboratory, opioids typically have an inhibitory effect on the firing of the nerve cells they interact with. Upon binding to opioid receptors on the cell membrane, the drugs, like their endogenous relatives, lead to an increase in the charge difference between the interior and exterior of the cell. This hyperpolarization makes it more difficult for the cell to depolarize and generate an action potential, or nerve impulse. (See [illustration](#).) Opioid receptors are dense in neurons involved in pain transmission, such as those in the dorsal horn of the spinal cord. By quelling the activity of these neurons, opioids block the sensation of pain.

"When you flood the system with a drug such as morphine, you switch on dampeners," says Clifford Woolf, a neurologist and neurobiologist at Harvard Medical School. And unlike other analgesics, which don't work for everyone and for all types of pain, "at high enough doses morphine is almost universal in its effect."

Because opioid receptors aren't just present along pain pathways, however, the drugs have some nasty side effects. In the brain stem, opioids can inhibit neurons that control breathing, contributing to suffocation during overdose. In the gut, the drugs can calm muscles of the digestive tract, leading to constipation for many opioid users. (See [illustration](#).) Another problematic side effect is tolerance—the longer a patient takes opioids, the more drug he needs to get the same amount of pain relief.

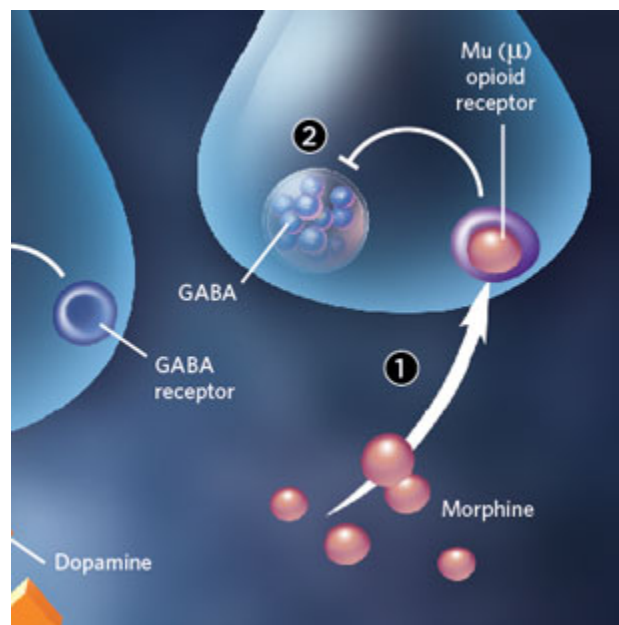
And, of course, the side effect with the biggest public-health impact: opioids are highly addictive.

Alex Peterson was 19 when he first experienced the intense high from opioids. He and his girlfriend had just broken up, and Peterson, who had been drinking and using drugs throughout his teens, turned to alcohol, consuming a liter of vodka a day. His drinking habit was so bad that he was coughing up blood and passing it in his stool. When he went to the doctor for a colonoscopy, the physician gave him an opioid painkiller called fentanyl during the procedure. "That's when I had my first, like, real rush of painkillers," Peterson, now 23, recalls. "I just remember coming out of that, it was such a euphoric, numbed-out feeling. It was definitely unlike anything else I'd had."

## In 2010, more than 16,000 people in the U.S. died of an opioid painkiller overdose.

Peterson became addicted to opioids—morphine, OxyContin, Dilaudid, heroin, anything he could get his hands on. Like many addictive substances, opioids tickle the brain's sweet spot, activating reward circuitry to encourage the continued use of the drug. Opioid drugs' target receptors are particularly dense in the limbic system, the part of the brain that is involved in emotions. Activation of opioid receptors in certain neurons leads to a release of dopamine from neurons in another brain region called the nucleus accumbens, giving users a high and a sense of happiness and well-being that can lead to dependence. (See [illustration](#).) "With an addict it's a craving, a hunger for something," Peterson says, "whether it's to get you out of your reality or take you out of your sickness."

### Receptors to the rescue



**THE HIGH:** Morphine's activation of the opioid receptor in neurons of the nucleus accumbens in the brain reigns in the release of the neurotransmitter γ-aminobutyric acid (GABA). This drop in GABA causes a neighboring cell to expel dopamine, which in turn elicits the euphoria associated with opioids.

**See full infographic:** [JPG](#) | [PDF](#) © THOM GRAVES One way that some scientists aim to curb opioid abuse is to uncouple the drugs' reward signals from their analgesic effects, possibly by targeting different opioid receptors. There are three types of opioid receptors, known as mu (μ), delta (δ), and kappa (κ), but pretty much every opioid painkiller in use today is thought to interact with the μ receptor, typically causing neurons to hyperpolarize and quiet down.

In the 1990s, a couple of mouse studies showed that blocking the activity of  $\delta$  opioid receptors seemed to reduce the tolerance and dependence associated with opioids that activate  $\mu$  receptors. Fourteen years ago, Andrew Coop, the chair of the pharmaceutical sciences department at the University of Maryland School of Pharmacy, set out to make a drug that fit the bill. "My approach was to design a single molecule that binds to  $\mu$  and acts as an agonist"—activating the receptor and depolarizing the cell as opioids normally would—"and binds to  $\delta$  as an antagonist" to inhibit its activity, he says.

After more than a decade of work, Coop finally found his answer: UMB 425, a synthetic derivative of a naturally occurring opioid. "[UMB 425] has the correct profile," he says, and so far, animal studies are yielding promising results. His team synthesized UMB 425 from thebaine, a natural opioid used to make oxycodone and other drugs. The big difference is a hydroxymethyl group attached to the opioid skeleton. The compound appears to be just as potent as morphine in pain assays in mice, but after five days on the drug, the animals display far less tolerance—"nowhere near [what] we see with morphine," Coop says.

Why a drug with dual targets has fewer side effects is not entirely clear, he adds. "No one knows. That is an open debate."

Medicinal chemist Philip Portoghese of the University of Minnesota College of Pharmacy was among the first to report that targeting  $\mu$  receptor activation while inhibiting  $\delta$  activity reduces drug tolerance. He says the effects of opioids on neurons are more complicated than the activation of individual opioid receptors. Evidence is emerging that opioid receptors can also form heteromers—complexes of receptors—and that opioid drugs can bind these structures. Morphine, for instance, appears to activate a heteromer of  $\mu$  and  $\delta$  receptors in addition to stimulating  $\mu$  receptors alone.

This could explain why Coop's drug helps to reduce tolerance. UMB 425 may be blocking the  $\delta$  receptor that opioids activate as part of  $\mu$ - $\delta$  complexes. "Most investigators weren't thinking of the combination of receptors" as drug targets, says Portoghese. "It's another level of complexity."

Developing drugs with receptor complexes in mind could yield those sought-after compounds that disrupt the usual opioid activation of reward or tolerance pathways, Portoghese proposes. Recently, his team published findings on a new drug candidate, MMG22, that acts as both an agonist for the  $\mu$  opioid receptor and an antagonist of the metabotropic glutamate receptor 5, which binds the excitatory neurotransmitter glutamate. MMG22, derived in part from the opioid oxymorphone, is believed to target a heteromer of the two receptors, which are both expressed in neurons in the dorsal horn, a region of the spinal cord that receives sensory information and is important in pain transmission.

In mice, MMG22 was extremely effective in blocking pain.<sup>2</sup> "It's the most potent analgesic that we've discovered . . . more than any that we have seen in the literature," says Portoghese. More importantly, "it has no tolerance." In other words, his group developed a drug many times more powerful than morphine that doesn't require higher and higher doses with long-term use. Finally, the drug works in animal models of inflammation, a type of pain that isn't always well treated with opioids.

The downside of the drug is that it is too big to cross the blood brain barrier—unlike Coop's drug, which is a small molecule—so it must be injected directly into the central nervous system, rather than taken orally. And because of the study design, the team wasn't able to test if the rodents became dependent on MMG22. Nevertheless, a University of Minnesota translational team is now moving the drug forward to see how it performs in humans.

Portoghese's group has also developed another molecule, called NNTA, that activates  $\mu$  opioid receptors only when they are in tandem with a  $\kappa$  opioid receptor. In human embryonic kidney cells having only  $\mu$  opioid receptors, the compound acts as an antagonist, plugging up the receptor. The drug is an extremely potent painkiller when injected into the mouse spinal cord, plus, it shows "really little, if any, physical dependence," says Portoghese.<sup>3</sup>

## Beyond neurons

Neurons are not the only cells involved in pain. In the past few years, new evidence has implicated glial cells, which serve a number of important roles in the central and peripheral nervous systems, in pain.

"We, and now others, have come to the same conclusion that immune-like glial cells are activated in every model of pain," says Linda Watkins, a neuroscientist at the University of Colorado Boulder who has been banging the glial drum for some time. "Block them, and you block pain in every clinically relevant animal model."

One approach to blocking the activity of glia is by jamming up toll-like receptor 4 (TLR4). When activated in glia, this receptor amplifies pain signals by causing the release of neuroexcitatory substances, Watkins says. It turns out that some opioids, including morphine, activate TLR4, dampening their own pain-killing effects. Logic would then dictate that blocking TLR4 might enhance the analgesic effect of an opioid.

Without knowing for sure what would happen, Watkins and her colleagues tested the idea on rats. They used (+)-naloxone, a stereoisomer of an approved drug used to treat opioid overdoses. A TLR4 antagonist, (+)-naloxone has no effect on the opioid receptor. When rats were given morphine following (+)-naloxone, "morphine is able to suppress pain, but not able to activate glial cells," Watkins says.

**We're caught between trying to medicate people in pain and trying not to exacerbate the epidemic.**—Dave Thomas, National Institute on Drug Abuse

Remarkably, and for reasons that remain unclear, the drug combination doesn't seem to tap into the brain's reward network.<sup>4</sup> In particular, the combo-treated animals had no "place preference" for morphine, a commonly used measure in which animals favor a particular chamber within their enclosure where a drug was given. Watkins is now working on a proposal to the FDA to start moving (+)-naloxone through the clinical-trial process.

## New targets



**OPIOID RECEPTORS IN THE BODY:** Opioid receptors are dispersed throughout the body, but a few key regions are involved in the major effects (and side effects) of opioid drugs.

**See full infographic:** [JPG](#) | [PDF](#) © ERAXION/ISTOCKPHOTO.COM Despite these successes in the lab, some worry that targeting the opioid receptor is like playing with fire. A number of researchers, including Harvard's Woolf, are looking in new directions, such as targeting cannabinoid, capsaicin, and other receptors to ease pain. "My own attitude is rather than trying to play with the opioid receptor system, look for completely alternative strategies," he says.

Woolf points to a number of promising avenues. Sodium channels uniquely expressed in pain fibers look attractive as drug targets, he says, and certain subunits of calcium channels enriched in pain pathways are also attractive. Researchers recently published evidence that a compound in centipede venom works better than morphine to quell pain in rodents, for example; the venom's target is a sodium channel whose function is lost in people who don't sense pain.

Marijuana has also gained considerable support as states have pushed to make the drug more accessible to people in pain. Looking to seize upon the painkilling power of cannabinoids, Dale Deutsch of Stony Brook University and his colleagues screened a million compounds to find those that would inhibit the enzyme that breaks down anandamide, an endogenous cannabinoid neurotransmitter. The result is an increase in anandamide, which activates natural cannabinoid receptors, and which Deutsch's group found has painkilling powers.<sup>5</sup>

His team is now working to develop a medicine from these compounds, but it is unlikely that they could be as effective as opioids. Developing a less effective drug is a tough sell, but there are other advantages, such as safety, Deutsch notes. "If you overdose with this or marijuana, your heart doesn't stop, your breathing doesn't stop. People are dying from [opioids]."

## **REMAKE**

**Why start from scratch? Some companies are reformulating approved drugs to make them more difficult to snort and inject.**

Recognizing that getting a new medication on the market is a monumental and expensive task, some pain researchers argue that a more promising solution to the opioid problem is to simply improve the drugs we've got. "Coming up with a new formulation is easier to get through the regulations than coming up with a new drug," says Andrew Coop of the University of Maryland.

In the early 2000s, when researchers at Purdue Pharma, the maker of OxyContin, recognized the severity of the situation regarding painkiller abuse, "we dropped many other projects to focus on the reformulation of OxyContin," says Jennifer Giordano, the company's director of analytics. At first they tried to combine the drug with the opioid antagonist naloxone, but the program was stopped because of safety concerns.

So the Purdue team turned to abuse-deterrent technology and quickly discovered that, when included in a drug's formulation, a high-weight polymer called polyethylene oxide makes pills more difficult to crush. When water is added, the chalky pill contents turn into a goopy mess, making intravenous injection all but impossible.

In April 2010, the FDA approved Purdue's reformulated version of OxyContin, which was in pharmacies by August of that year. Then came the real test: Would opioid abuse actually be discouraged? So far so good, according to the company's tracking of the drug's use. "[Our epidemiologic studies] all consistently show a positive effect of reformulation," says Paul Coplan, the executive director of risk management and epidemiology at Purdue. Reports of deaths and drug overdoses related to OxyContin



declined considerably after the new version came out, he says, and OxyContin abuse dropped by as much as 41 percent among a group of drug users, according to a Purdue study published last year.<sup>1</sup>

The company is motivated by its reformulated OxyContin, which is currently the only prescription opioid with abuse-deterrent technology that the FDA recognizes as effective in actually deterring abuse, and has pledged to make similar adjustments to each of its opioid products.

Other companies are also developing their own formulations, but so far none have succeeded in convincing the FDA of the drugs' ability to curb abuse. Pfizer, for instance, has incorporated a nasal irritant developed by Acura Pharmaceuticals into its oxycodone drug, Oxecta, so that the drug burns the nose if snorted. "It's similar to what chili powder would do, although the ingredient is not capsaicin in this case," says Albert Brzezcko, the vice president of technical affairs at Acura.

But a little burning isn't always enough to dissuade abuse. In a clinical trial, Acura asked recreational drug users to compare the likability of a hydrocodone drug to the same drug that included the irritant. The participants initially preferred the unadulterated high, but over time, they liked the modified Oxecta just the same. Acura is now working to tweak the drug so that the irritant's aversive effects peak at the same time as the pleasurable feelings of the opioid high.

Last year the FDA published guidelines to help companies develop abuse-deterrent drugs, though the agency does not require companies to include such technology in their opioid products. As a result, new abusable opioids continue to come on the market—sometimes against the recommendations of the FDA's own drug-safety and risk-management advisory committee. "Our number one concern was the lack of abuse-deterrent formulation" in a newly approved opioid drug called Zohydro ER, says Jeanmarie Perrone, a member of the committee and an emergency physician at the University of Pennsylvania Health System. When Zohydro ER, which could be subject to more abuse than OxyContin, was approved last October, despite the committee's vote against approval, Perrone says she "was disappointed and surprised and concerned."

Others liken reformulation to rearranging deck chairs on the Titanic. There's some evidence that abuse-deterrent reformulations only send users elsewhere—to heroin, in particular. Alex Peterson, who has been sober for two years and is part of a program that supports students with addictions at Augsburg College in Minneapolis, says he's never met an addict who wasn't up for a challenge. "If [companies] come up with special formulas, it's just going to [get] people to use something else."

1. S.F. Butler et al., "Abuse rates and routes of administration of reformulated extended-release oxycodone: Initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment," *The Journal of Pain*, 14:351-58, 2013.

## References

1. J.R. Healy et al., "Synthesis, modeling, and pharmacological evaluation of UMB 425, a mixed  $\mu$  agonist/ $\delta$  antagonist opioid analgesic with reduced tolerance liabilities," *ACS Chem Neurosci*, 4:1256-66, 2013.
2. E. Akgün et al., "Ligands that interact with putative MOR-mGluR5 heteromer in mice with inflammatory pain produce potent antinociception," *PNAS*, 110:11595-99, 2013.
3. A.S. Yekkirala et al., "N-naphthoyl- $\beta$ -naltrexamine (NNTA), a highly selective and potent activator of  $\mu/\kappa$ -opioid heteromers," *PNAS*, 108:5098-103, 2011.
4. M.R. Hutchinson et al., "Opioid activation of toll-like receptor 4 contributes to drug reinforcement," *J Neurosci*, 32:11187–200, 2012.
5. W.T. Berger et al., "Targeting fatty acid binding protein (FABP) anandamide transporters – A novel strategy for development of anti-inflammatory and anti-nociceptive drugs," *PLOS One*, 7:e50968, 2012.