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Because opioids can shut down breathing, overdoses are often fatal without medical intervention.

New painkillers could thwart opioids' fatal flaw

By Meredith Wadman | Nov. 16, 2017, 12:00 PM

When people die from overdoses of opioids, whether prescription pain medications or street drugs, it is the suppression of breathing that almost always kills them. The drugs act on neuronal receptors to dull pain, but those in the brain stem also control breathing. When activated, they can signal respiration to slow, and then stop. The results are well-known: an epidemic of deaths—about 64,000 people in the United States alone last year.

Countering this lethal side effect without losing opioids' potent pain relief is a challenge that has enticed drug developers for years. Now, for the first time, the U.S. Food and Drug Administration (FDA) in Silver Spring, Maryland, is considering whether to approve an opioid that is as effective as morphine at relieving pain and poses less risk of depressing breathing.

Trevena, a firm based in Chesterbrook, Pennsylvania, announced on 2 November that it has submitted oliceridine, an intravenous opioid meant for use in hospitalized patients,

to FDA for marketing approval. The drug, which would be marketed under the name Olinvo, is the most advanced of what scientists predict will be a growing crop of pain-relieving "biased agonists"—so called because, in binding a key opioid receptor in the central nervous system, they nudge it into a conformation that promotes a signaling cascade that kills pain over one that suppresses breathing. And in a paper out this week in *Cell*, a veteran opioid researcher and her colleagues unveil **new biased opioid agonists that could surpass oliceridine**, though they haven't been tested in people yet.

"There are many groups creating [such] biased agonists. And one of them is going to get it right," says Bryan Roth, a molecular pharmacologist at the University of North Carolina in Chapel Hill. "To have a drug you can't die of an overdose with would be a huge lifesaver for tens of thousands of people every year."

Trevana's compound is by far the closest to the finish line, having been through clinical trials. The firm has had setbacks, however. In phase III trials in postsurgical patients reported in February, oliceridine proved to be as effective a painkiller as morphine, and quicker to act. But although a low dose of it caused less respiratory suppression and fewer other side effects than morphine, those improvements didn't reach statistical significance for higher doses.

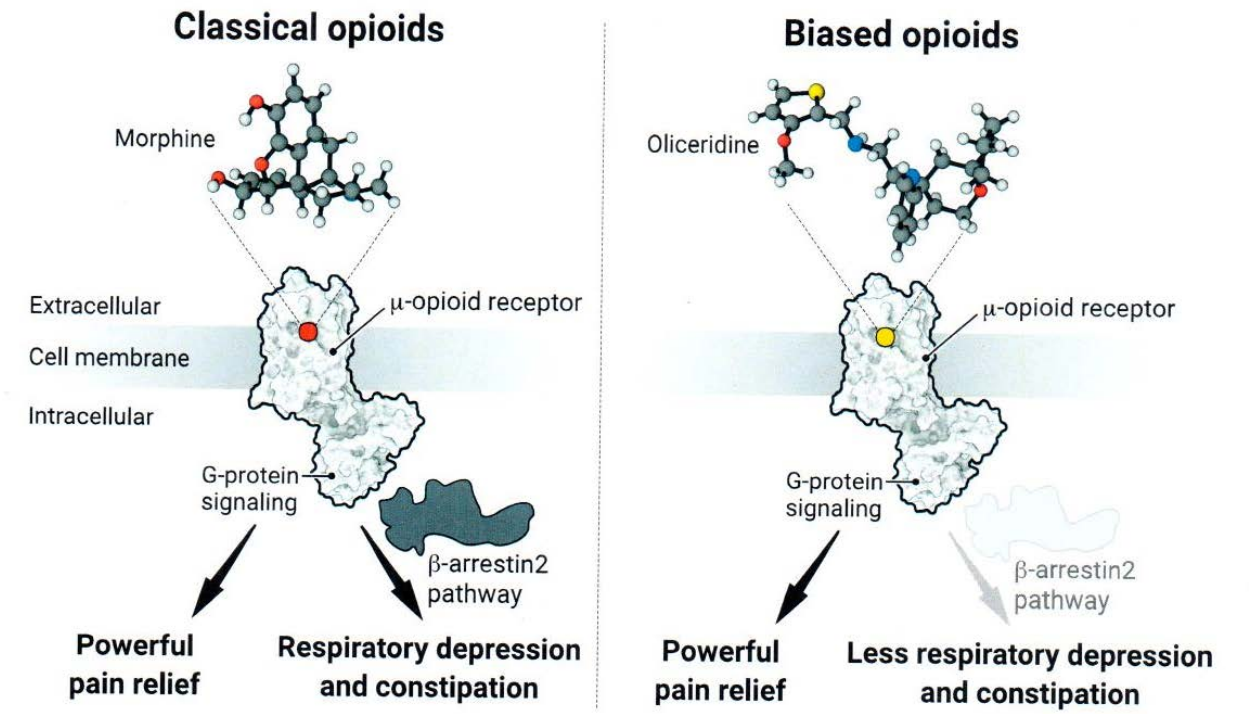
The competition aims to catch up quickly. Last month, Mebias Discovery in Philadelphia, Pennsylvania, presented data on two new biased opioids that protected breathing in rats even at four times the effective painkilling dose. It hopes to begin human trials of one of them as soon as 2019.

For most of these early-stage drugs, developers haven't assessed just how selectively they trigger the painkilling pathway over respiratory suppression. Nor have they shown conclusively that the molecular bias matters—that the more biased a compound toward triggering the painkilling pathway, the less the risk of respiratory suppression. But the *Cell* study this week has done both, at least in mice.

In that work, neuroscientists Laura Bohn, Cullen Schmid, Thomas Bannister, and their colleagues at the Scripps Research Institute in Jupiter, Florida, developed several pain-killing-biased compounds from among scores that bind the μ-opioid receptor. Activating this protein, which is embedded in neuronal cell membranes, leads to either pain relief or respiratory depression depending on the brain circuit to which it belongs. The molecule is known as a G protein-coupled receptor because it triggers so-called G proteins to bind to the inner side of a receptor and start a signal cascade.

Bias toward breathing

A new generation of opioids aims to stall the signaling that is thought to shut down the lungs during overdoses.



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When traditional opioids—such as morphine, fentanyl, and heroin—activate the receptor, that also attracts an intracellular protein called β-arrestin2. It tamps down G-protein signaling, so that the message doesn't remain indefinitely "on." But β-arrestin2 also helps produce the respiratory suppression and constipation that are hallmark side effects of opioids.

Beginning 18 years ago, Bohn and her colleagues showed that, in mice engineered to lack β-arrestin2, morphine's pain relief was stronger and longer-lasting and its main side effects were dramatically reduced. The mechanism by which β-arrestin2 leads to an opioid's unwanted effects remains unclear. But it seemed to many researchers that if drugs could be created that nudged the μ-opioid receptor into a conformation that shut down β-arrestin2 recruitment while turning on G-protein signaling, they might deliver opioids' unparalleled pain relief without those side effects.

In the new study, Bohn's group used cell signaling assays on a library of μ-receptor-activating compounds to find a few with hints of a bias toward G-protein signaling. Based on the structural features of those leads, they tweaked the compounds to create scores that were more heavily biased. They chose six to study in mice, and discovered all had effective antipain activity. As important, the greater the compound's bias for G-protein-signaling, the fewer breathing problems it produced in the animals.

The study is "very rigorous and formalized. And it's pretty remarkable. Essentially the more G-protein biased, the less respiratory depression. In other words, the safer," Roth says. The paper "is a tour de force," for its labor-intensive validation of concepts that

had only been inferred from smaller studies, says molecular pharmacologist Gavril Pasternak of the Memorial Sloan Kettering Cancer Center in New York City.

Other academic groups are chasing biased opioids. A team including Roth and Brian Shoichet, a chemist at the University of California, San Francisco, who uses computer simulations to find new drugs, last year published details of a powerfully G-protein-biased μ-receptor agonist, PZM21. It kills pain in mice and doesn't depress breathing. In its 2016 paper, which appeared in *Nature*, the group also reported that PZM21 appeared to be less rewarding in mice. That suggests it could be less addictive in people, though further studies are needed, says Roth, who holds founder stock in a San Francisco startup, Epiodyne, aiming to develop the compound further.

Some doubt that PZM21 will turn out to be less prone to abuse in humans. That suggestion doesn't line "up with the basic science and certainly does not describe our own data on Olinvo," says Jonathan Violin, a molecular pharmacologist who co-founded Trevena and is now one of its vice presidents.

For biased opioids in general, "The $64,000 question is: What about dependence?" says Robert Lefkowitz, a biochemist at Duke University in Durham, North Carolina, who shared the 2012 Nobel Prize in Chemistry for work on G-protein-coupled receptors, and who co-authored Bohn's first paper on β-arrestin2 knockout mice. Lefkowitz, who owns founder shares in Trevena and stands to make money if Olinvo succeeds, says there is little evidence that tamping down β-arrestin2 will blunt the agonizing physical withdrawal symptoms that set in when someone tries to kick an opioid habit.

Bohn plans to evaluate the addictiveness of her stable of compounds in an upcoming study. But first, she is probing whether heavily G-protein-biased opioids can slay another bugbear of these medicines: tolerance, which is the need for increasing, and ever-riskier, doses of a drug to achieve the same amount of pain relief. "So far," she reports, "it's looking really promising."

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