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Innovations

Janus-Faced Drugs:
The Double-Edged Synthetic Opiate Trade

"Pain has an absolute meaning," says Martin Angst, Assistant Professor of Anesthesia at the Stanford University School of Medicine. Pain is a critical warning system, signaling threats to the body. If you are a cancer patient, pain can signal progression of disease. It is related to your emotional and physical state; if you are tired, pain can be much more severe than if you are well rested. Pain can also become a self-propagating process or a disease of its own, remaining long after the original trauma is past. Chronic pain not only threatens a person's physical well-being but also his or her mental health. As a consequence, treating chronic pain without producing side effects and drug dependence is one of the more difficult problems facing modern medicine.

A 40-min drive from Stanford's campus is a South San Francisco biotech company with an intriguing approach to the tradeoffs in pain treatment for patients with chronic moderate to severe pain. Pain Therapeutics, http://www.paintrials.com/, founded in 1998, is developing new opiate-based drugs that cause fewer side effects and are less likely to induce dependence than conventional opioids. In a nod to its historical antecedents, Pain Therapeutics' annual report is illustrated with nineteenth-century vignettes of opium production and patent medicines.

To date, the company's three products, Remoxy, Oxytrex, and PT-901 (for treating irritable bowel syndrome) are all in stage III clinical trials. Remoxy and Oxytrex are being presented for broad label FDA approval. Remoxy is a sustained-release, less abusable form of the pain reliever Oxycontin. Remoxy's gel caps, developed with technology licensed from Durect Corporation, contain opiate formulated in a viscous gel to absorb into the body slowly, preventing the "high" sensation. The patented gel also makes extraction of oxycodone, 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, the active ingredient by crushing, chewing, or leaching it out and concentrating it more difficult.

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Oxytrex combines an extremely low dose of naltrexone, an opiate receptor antagonist, with oxycodone. Rat studies conducted by Pain Therapeutics [1] show Oxytrex has an increased analgesic efficacy or potency with decreased addictive potential. According to the company's stage III human and animal studies, patients are less likely to develop tolerance to the drug, which means they won't have to increase the dosage to get the same pain relief through extended use. "So basically, you get more of the analgesic effect, which is what you want out of the opioid, with fewer problems," says Lindsay Burns, researcher at Pain Therapeutics.

Opium has been used by humankind since prehistoric times, according to Martin Booth's book *Opium, A History* [2]. A sample of opium was found in the tomb of Cha in Egypt, dating from the fifteenth century BC. Opiate is the generic term for a family of alkaloids that is derived from natural opium. Modern semi-synthetic drugs are modified opium alkaloids. Laudanum, a tincture of opium and alcohol, was developed in the 1660s and stayed popular as a sedative and medication over the centuries. Unfortunately, it was unpredictable in its effects because of the variation in the relative concentrations of the various opiate alkaloids in the raw opium. In the 1800s, Friedrich Wilhelm Adam Sertürner, a German pharmacist's assistant, looking for a more reliable remedy, isolated morphine, (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol, the principal active ingredient in raw opium. Codeine, (5α,6α)-7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol or methylmorphine, a less powerful and less addictive substance, was synthesized in 1832 by Robiquet followed in 1874 by British pharmacist C.R. Alder Wright who synthesized diacetylmorphine, which was mass produced and marketed by Bayer under the brand name "heroisch," heroic or heroin, at the turn of the century. Methadone (6-[dimethylamino]-4,4-diphenyl-3-heptanone) was synthesized at I.G. Farben at Hoechst-am-Main in Germany during World War II. Methadone is a completely synthetic opioid with a long-lasting effect. It is an analgesic that is primarily a mu-opioid receptor agonist that has no resemblance to the chemical structure of morphine but which produces similar effects. Oxycodone is a semi-synthetic opiate analgesic in clinical use since 1917 that is pharmacodynamically comparable to morphine. Purdue Pharmaceuticals (Stamford, CT) patented Oxycontin, a controlled release oxycodone, in 1995, but the formulation has been notoriously popular with recreational abusers.

The Road to Prime Time

"The pain space is something that I've had my eye on since about 1985," says Remy Barbier, CEO and founder of Pain Therapeutics. "I've always found it unbelievable that the standard of care used to treat chronic pain today is the exact same drugs that our great-great grandparents used. I don't understand why huge pharmaceutical companies with huge resources have not invested in this area 50 years ago."

About 12 years ago, Barbier came across research conducted at the Albert Einstein College of Medicine under Dr. Stanley Crain, now Professor Emeritus of the Department

of Neuroscience. Crain's research showed that opiates had dual properties: they not only inhibited pain, but also had an excitatory effect that could be mediated by a group of opiate receptors. During chronic use, the excitatory effect becomes more pronounced and counteracts to some degree the pain-inhibiting ability of the opiate. In the early 1990s, Crain's group went further and discovered that by administering ultra-low doses of naltrexone (an opiate receptor antagonist) with the opiates, they could selectively block the excitatory effects of opiates in mice while increasing analgesic effects [3]. Barbier thought it was "very intriguing, but not ready for prime time."

Four years later, Barbier got a phone call. Crain invited him to visit his lab. "I flew out to New York and spent a few days there and thought, 'Holy cow, this guy really followed through!'" Barbier recounts. With an initial personal investment of one million dollars, Barbier was able to attract three rounds of venture capital and go public. "Seven years later, we have a pipeline of three drugs and all are in phase III," Barbier says. "To deal with the two main problems with opioids, safety and physical dependency, we developed Remoxy, which is a less abusable form of a $2 billion drug. The other drug we have, Oxytrex, is a more efficacious form of a $2 billion drug."

Opiates have always been a high-risk, high-reward business, and indeed Pain Therapeutics' annual report states: "Drug development is not for the impatient or impoverished." According to its June 30, 2005, financial report, the company has taken in $206 million in IPO and venture money, has spent cumulatively $130 million, and has $81.7 million cash and marketable securities. Now in stage III clinical trials for its candidates, the company is burning about $40 million a year for research and development and administrative expenses. Pain Therapeutics owns the commercial property rights to its drug candidates, and the company is targeting the over $3 billion pain market projected to grow as baby boomers age.

Angst on Pain

"We call opiates a double-edged sword or Janus faced," says Angst. "They do a lot of good and potentially a lot of harm as well." Opiate side effects include respiratory depression, sedation, constipation, itching, nausea, reduced functioning, physical dependence, and in some cases, addiction. "More recently, we have learned that opioids somewhat paradoxically can increase the sensitivity to pain," says Angst. "These side effects are more likely to occur at higher doses."

According to Angst, 10 or 20 years ago opioids were predominantly prescribed only for patients suffering from acute pain or for palliative care for the dying because of concerns about turning patients into addicts. Angst says that most people exposed to opiates become dependent, but they do not become addicted. "Being dependent on an opioid means that if you don't get the drug you will develop signs of withdrawal," Angst says. "Being addicted means that you have an urge to get the drug. Nicotine is actually a much more addictive substance than opioids."

"The concept [behind Pain Therapeutics] is that a receptor can be inhibitory or excitatory depending on the amount of drug available at the receptor site," says Angst. "According to this, it makes sense to give a very small amount of opiate antagonist to block the excitatory effects, thus making the opiate only exert inhibitory effects, inhibiting pain. However, the validity of this concept is controversial and by no means yet established. Studies trying to voice this principle have mixed results. I cannot say that the principle they are trying to exploit is flawed. It is a hypothesis, and I have not seen enough scientific evidence to robustly predict that the exploited principle will work clinically. Optimizing the use of opioids is a complex undertaking. The approach pursued by Pain Therapeutics is definitely innovative but lacks broad scientific backing. It does address something important: how can we take advantage of the beneficial effects of opiates and minimize or avoid the [adverse] effects?"

Opioids work so well because they mesh into the body's own pain system and receptors. "Your body has natural narcotics [endorphins]. Everybody has natural receptors in the spinal cord and brain. People have come up with substitutes. None are very good," says Dr. Carol A. Warfield, Chief of Anesthesia, Critical Care and Pain Medicine at Beth Israel Deaconess Medical Center in Boston. "For a long time, it was thought that if you gave people opiates, they would get addicted," Warfield says. "It was common for doctors to under-medicate patients for pain. 10 or 15 years ago, it became evident that many people don't need an increase in opiate dosage over time like we thought they would."

Currently, doctors can rotate patients between roughly three classes of opiates to avoid tolerance or dependence: the Methadone group, the Demerol group (meperidine and fentanyl), and the group that includes morphine and codeine. Doctors also use opiate adjuncts, such as nonsteroidal anti-inflammatories like ibuprofen for arthritis and anticonvulsives and antidepressants for nerve pain. Warfield says that the pain program uses a whole gamut of procedures to deal with pain, including acupuncture, hypnosis, and spinal stimulators. "We tend to use opiates as a last resort," Warfield says.

It is now prime time for Pain Therapeutics. Remoxy and Oxytrex are being presented before the FDA. However, Merck's withdrawal of Vioxx and the FDA's suspension of Bextra (both COX-2 inhibitors) for clarification of long-term side effects may cast a shadow on FDA approval for new pain drugs. But Pain Therapeutics is using well-established drugs, preapproved by the FDA, and putting them in different formulations.

"This is not a get rich quick type of business," Barbier says. "If you are not passionate about the science and the end points, don't bother. There are no shortcuts."

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