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Novel Paths to Pain Relief at Neuroscience Annual Meeting

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With 230 million prescriptions written annually, opioid drugs are “the drug of choice for addressing severe pain,” session moderator Allan Basbaum, from the University of California at San Francisco, told reporters this week at a press conference on new approaches to pain relief at the annual meeting of the Society for Neuroscience.

But their societal cost is sobering. Highly addictive and dangerous, the overdose death toll from prescription painkillers now exceeds that from heroin and cocaine combined. Consequently, Basbaum said, “addressing their side effect profile is one of the essential steps to make those drugs more effective.”

The silver lining is that the analgesic effects of such drugs can possibly be separated from their addictive effects.

That’s the goal of San Francisco-based Nektar Therapeutics Inc., which is working on opioid receptor agonists that retain their effectiveness as painkillers, but not their ability to get users high. The team presented data on its preclinical compound NKTRI92 at the annual meeting this week.

The reason addictive drugs are addictive is that they cross the blood-brain barrier extremely rapidly, essentially flooding the brain, which leads to a feeling of euphoria.

Other companies have tried to get rid of opioids’ euphoric effects. But, Nektar Chief Medical Officer Robert Medve told *BioWorld Today*, “one thing all of the abuse deterrents have in common . . . is that they are all about delivering a known opioid. So at the end of the day, it is possible to liberate that opioid” – and addicts can bring a lot of ingenuity to such liberation strategies.

In contrast, NKTRI92 “looks like a sustained-release formulation” in its uptake rate. “But it’s not a formulation” – and so, “there’s nothing to crush” for an addict to get a part of the drug that can deliver a rush.

Instead, NKTRI92 is an opioid receptor agonist, but is not similar in its structure to opioids themselves. In addition, the drug is conjugated to a biopolymer that further slows down its uptake into the brain.

In brain cell perfusions, Stephen Harrison, Nektar vice president of research biology, told reporters at the press conference, “we see less than 10 percent of the rate of entry of oxycodone,” which is the opioid component in painkillers like Percocet.

“We never say that this has no abuse liability,” Medve said. But “when you slow down the entry [into the brain], you make it less attractive.”

In animal experiments, NKTRI92 was an effective painkiller. But as a result of its slow uptake, Harrison said, “rats will not work any harder [to get an injection of NKTRI92] than they would to get a saline solution injection,” which is a way to gauge a drug’s abuse potential.

Overall, Harrison said at the press conference, NKTRI92 “has full pain relief and in animal models shows low abuse potential.”

The company hopes to enter the clinic with NKTRI92 in the first half of 2012; a related drug, NKTRI81, is in Phase I trials.

Instead of improving the properties of opioids, other companies are developing alternatives to them.

Already in the clinic is an approach developed by Swedish biopharmaceutical company Diamyd Medical AB: the use of gene therapy to block pain sensation in peripheral nerves that is transmitted back to the spinal cord.

At the meeting, David Fink, of the University of Michigan, reported results from that Phase I trial. In the trial, 12 patients with chronic cancer pain received the NP-2, which consists of the gene for enkephalin, a peptide that acts as a natural painkiller, delivered via a viral vector.

As a Phase I trial, the main issue and primary endpoint of the trial was to look for adverse events, of which there were no major ones.

But the trial also managed to show what Fink termed a “substantial and dose-dependent reduction in perceived pain: Patients receiving the highest dose of NP-2 reduced their subjective pain ratings from eight out of 10 (despite

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being treated with morphine) before treatment to two out of 10 after.

Fink noted that the trial was small and neither blinded nor placebo-controlled, and so what could be gleaned from the trial data were “interpretations, not conclusions.” But those interpretations, “suggested – to the sponsor at least – that NP-2 might be effective in reducing pain.” Diamyd is currently in Phase II trials with the approach.

Finally, in preclinical studies, researchers from the Cleveland Clinic described what they hope may be an approach to treating the pain associated with spinal cord injury.

Persistent intractable pain,” moderator Basbaum told the audience, “is one of the major consequences of spinal cord injury,” befalling as much as 90 percent of the 14,000 patients who injure their spinal cords each year.

In fact, a substantial number of those patients will rate

pain relief as a higher priority than regaining the ability to walk.

In their study, the researchers treated rats with fibronectin – a protein that can be found in the scar tissue that forms after a spinal cord injury and appears to help regulate inflammation and neuronal survival.

They found that such treatment was effective against allodynia, where benign stimuli suddenly become painful, but not hyperalgesia, where painful stimuli become more painful.

But the most spectacular aspect of their data was how long the treatment effect lasted: for up to eight months, which, in terms of its proportion of the average rat life span, works out to about 25 years.

That duration, presenter Ching-Yi Lin told reporters, makes it “the longest and strongest inhibition effect ever reported in animal studies.” ■