Commentary: Per von Mentzer

A new opioid drug for chronic pain is in development

Opioid drugs have been a primary treatment for acute and severe pain for decades. In the US, the first synthetic opioid medicines were developed just after the start of the 20th century and since that time have been closely regulated by the US Food and Drug Administration. However, the widespread overuse of opioid prescription drugs like oxycodone has led to a devastating public health crisis because of their addictive nature, and potentially fatal side effects. In the US alone, opioid overdoses claimed the lives of more than 100,000 people in 2023, with prescription painkillers playing a significant role in the epidemic. The damage done to victims led to a settlement of $7.4 billion by the owners of the Purdue company that supplied many of these drugs. Unsurprisingly both regulators and companies are looking for new approaches for treating pain.

One approach is to develop non-opioid drugs. On 30 January, the FDA announced the approval of Journavx (suzetrigine) the first in a new class of non-opioid analgesics that reduces pain by targeting a signalling pathway involving sodium channels in the peripheral nervous system.

A second approach is to develop more sophisticated opioid products with a much safer profile. This is what our Sweden-based company PharmNovo AB is doing with its lead product, PN6047, which is currently in Phase 2 clinical development. This article gives a summary of the concept behind the product and the work that has been done thus far.

Conventional opioids, like morphine and oxycodone, act via one or more of the opioid receptors, mu (MOR), kappa (KOR) and delta (DOR), and most are selective for the MOR, activation of which is responsible for the beneficial effects in treating acute pain, but also for the unwanted effects which include nausea, constipation, itching and potentially fatal respiratory depression. They also have a euphoric effect that is the basis for non-medical use and, frequently, addiction. Repeated use of opioids can lead to opioid use disorder (OUD), a complex condition characterised by compulsive taking of the drugs, even when the user wants to stop. As opioid use continues, tolerance develops rapidly, meaning that users require higher doses to achieve the same level of pain relief or 'high.' This increases the risk of overdose and comes with the risk of respiratory depression and death.

Stopping conventional opioid use in the dependent individual is not straightforward as abrupt cessation results in an opioid withdrawal syndrome (OWS). Withdrawal flu-like symptoms, include increased pain sensitivity, muscle aches, sweating, nausea, vomiting, and diarrhoea, make quitting extremely difficult. Up to 20% of patients prescribed opioids for legitimate medical reasons become dependent.

Treatment for OUD and OWS typically involves opioid substitution drugs like methadone, which reduce withdrawal symptoms and cravings, but do not address the underlying issues of dependency and carry their own risks of misuse and keeping people addicted – now to methadone. Conventional opioids are not effective for treating chronic pain and there is an urgent need for alternative treatments for chronic pain, and potentially other conditions, that do not carry the same risks of addiction and the serious unwanted side effects of the conventional opioids.

PharmNovo's small molecule drug, PN6047, is a very selective delta opioid receptor agonist (DORA). PharmNovo's first target is neuropathic pain – a chronic pain condition caused by damage or dysfunction of the nervous system leading to abnormal pain signals. By focusing on DOR activation and avoiding MOR-mediated unwanted effects, PN6047 is shown to be potent, safe and effective, lacking the usual unwanted side effects associated with conventional MOR-targeting opioids. The drug is now advancing to Phase 2 proof-of-concept studies.

Neuropathic pain: an unmet medical need

Neuropathic pain is a chronic condition that affects up to 10% of the adult population worldwide. It is caused by injury or diseases affecting the nervous system, such as diabetes, shingles, multiple sclerosis or spinal cord injuries. Unlike acute pain, which serves a protective function, neuropathic pain persists in the absence of an ongoing injury, causing debilitating symptoms such as allodynia (pain on the skin from normally non-painful stimuli) and hyperalgesia (exaggerated pain response). These symptoms can severely impair mobility, mental health, and overall quality of life.

The complexity of neuropathic pain lies in its underlying mechanisms, which involve abnormal nerve signalling, inflammation, and alterations in the brain's perception of pain. This multifaceted pathology makes it particularly challenging to treat effectively. There are currently no drugs explicitly developed for neuropathic pain therapy. Current treatments, originally developed for depression or epilepsy — such as the antidepressant serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclics (TCAs), and anticonvulsants like gabapentin and pregabalin—offer only moderate relief and only in some patients and they are associated with a variety of potentially serious side effects. Although not recommended in national guidelines and treatment algorithms, conventional opioids might still be used in severe cases of neuropathic pain, but their high risk of dependence and overdose makes them unsuitable for long-term use.

The scientific inspiration behind PharmNovo came from Bengt von Mentzer, the company's founder and currently the chief scientific advisor. Dr von Mentzer has led the development of PN6047. He previously worked for more than 30 years at AstraZeneca Plc in pain research.

In comparison with the MOR, the DOR has been somewhat under-researched, but it is known to play critical roles in pain regulation, mood and immune function. Unlike the MOR, its activation does not come with the same risks of addiction, tolerance, or respiratory depression. PN6047 is more than 100,000 times more selective for DOR than MOR providing potent neuropathic pain relief without the side effects and

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abuse potential linked to MOR-targeting drugs.

For many years, DORA development was largely abandoned due to concerns about the perceived risks of anything classified as an opioid, and because drug-induced seizures were observed in a few early preclinical studies with 'first generation' DORAs. However, Dr von Mentzer believed there was untapped potential in DOR-targeting drugs and pursued research in this area together with Prof David Kendall, co-founder and the company's chief scientific officer, leading to the development of PN6047.

In addition to the marked receptor selectivity, PharmNovo has built something called agonist bias into the PN6047 molecule. Stimulation of the DORs can activate two major biochemical signalling systems that use G proteins or arrestin proteins. Unlike the early, 'first-generation' DORAs, which equally activate both G protein signalling (responsible for chronic pain relief) and arrestin pathways (linked to tolerance and dependence and possibly seizures), PN6047 is considered to be a 'second-generation' DORA which is G protein-biased, meaning that it selectively activates G protein signalling whilst minimising arrestin recruitment. This approach allows PN6047 to deliver sustained pain relief without the need for escalating doses, and without the risk of seizures, respiratory depression, or addiction.

Preclinical studies have confirmed PN6047's effectiveness in reducing neuropathic pain in rodent models. It significantly reversed pain caused by sciatic nerve ligation (SNL)—a widely used model of chronic nerve injury pain that induces persistent hypersensitivity, including mechanical hyperalgesia and allodynia. Notably, this pain relief was completely blocked by naloxone methiodide, a pan-opioid receptor antagonist that doesn't get into the brain, demonstrating that PN6047's pain-relieving effects are specifically mediated through peripheral targets, understood to be the sensory nerves. This is in contrast to the conventional opioids that also mediate their effects in the brain. This peripheral restriction contributes, along with its high selectivity and agonist bias, to the unique pharmacological profile of PN6047.

Extensive safety studies further validated PN6047's potential as a safer alternative to traditional opioids and the currently used drugs for neuropathic pain. Unlike conventional MOR-activating opioids, PN6047 did not cause respiratory depression, sedation, or motor impairment, and behavioural studies found no evidence of abuse potential in conditioned place preference tests, in drug-discrimination tests, and in self-administration tests, which are the 'gold standard' tests for evaluating addiction risk in preclinical research. Crucially, unlike earlier 'first generation' DORAs, PN6047 did not induce seizures, even at extremely high oral doses, thanks to its targeted action against the G protein pathway.

Also, PN6047 did not induce dependence or withdrawal symptoms upon discontinuation. In fact, it was effective in reducing the behaviours in animals withdrawn from repeated morphine administration in OWS models. This finding underpinned a project funded by the US National Institute on Drug Abuse (NIDA) in collaboration with researchers at Washington University and the University of Michigan. In addition to exaggerated pain, the OWS includes emotional disturbances (anxiety and depression) and migraine-like headache. Fascinatingly, PN6047 also produces antidepressant, anxiolytic and anti-migraine-like effects in the OWS and other preclinical models. These very promising results confirm the potential for treating OWS with PN6047 without the need for long-term opioid substitution therapy and further NIDA support for clinical evaluation is possible.

Although somewhat counterintuitive, the idea of treating components of the opioid crisis with an opioid, albeit with PN6047, whose pharmacology is quite distinct from the conventional opioids, is exciting and holds great promise for both patients and investors as a contribution to combatting the global opioid crisis.

Clinical trials

Following successful preclinical pharmacological and toxicological testing, PN6047 completed a first-in-human Phase 1 clinical trial, demonstrating a strong safety and tolerability profile in healthy human volunteers. PN6047 was well tolerated across all tested doses, with no signs of the common opioid-related side effects, such as respiratory depression, constipation, itching, or withdrawal symptoms. Importantly, pharmacokinetic analysis showed that PN6047 achieved plasma levels which are 30 times higher than the plasma levels required in preclinical models for maximum efficacy. This shows that human doses that are safe and tolerable are expected to provide effective pain relief in humans, reinforcing its potential as a promising treatment for neuropathic pain and other conditions.

Building on these very positive results, PN6047 is set to enter a phase 2a proof-of-concept (PoC) study in neuropathic pain patients, scheduled to begin by the end of 2025. Recognising its potential, the European Innovation Council (EIC) has awarded PharmNovo a €2.5 million grant, along with an equity opportunity of up to €15 million, to support further development and clinical progression.

Overall, the lack of development of DOR-selective drugs like PN6047 should be seen as a major missed opportunity by pharma, and, with the additional prospects identified in the preclinical literature for addressing neurodegenerative diseases, cardiac conditions, itching disorders and chronic cough, the future is bright and exciting.

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