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# A possible alternative to morphine – inspired by spit

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Opium poppies. Ruud Morijn Photographer/Shutterstock.com

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Would you take a painkiller that had been developed from human saliva? A recent study suggests you might in future.

Pain is an essential sensation. Sensory nerves with endings in our skin, tissues and organs, are activated by heat, cold or pressure, or by chemicals that are released from cells after tissue injury. The fibres of these nerves reach the central nervous system, activating neurons in the spinal cord which in turn connect with and activate neurons in a part of the brain known as the cerebral cortex. The cortex gives you the conscious perception of pain - that "ouch!" The system has evolved to produce a quick response. It takes a split second for you to withdraw your hand from a burning flame.

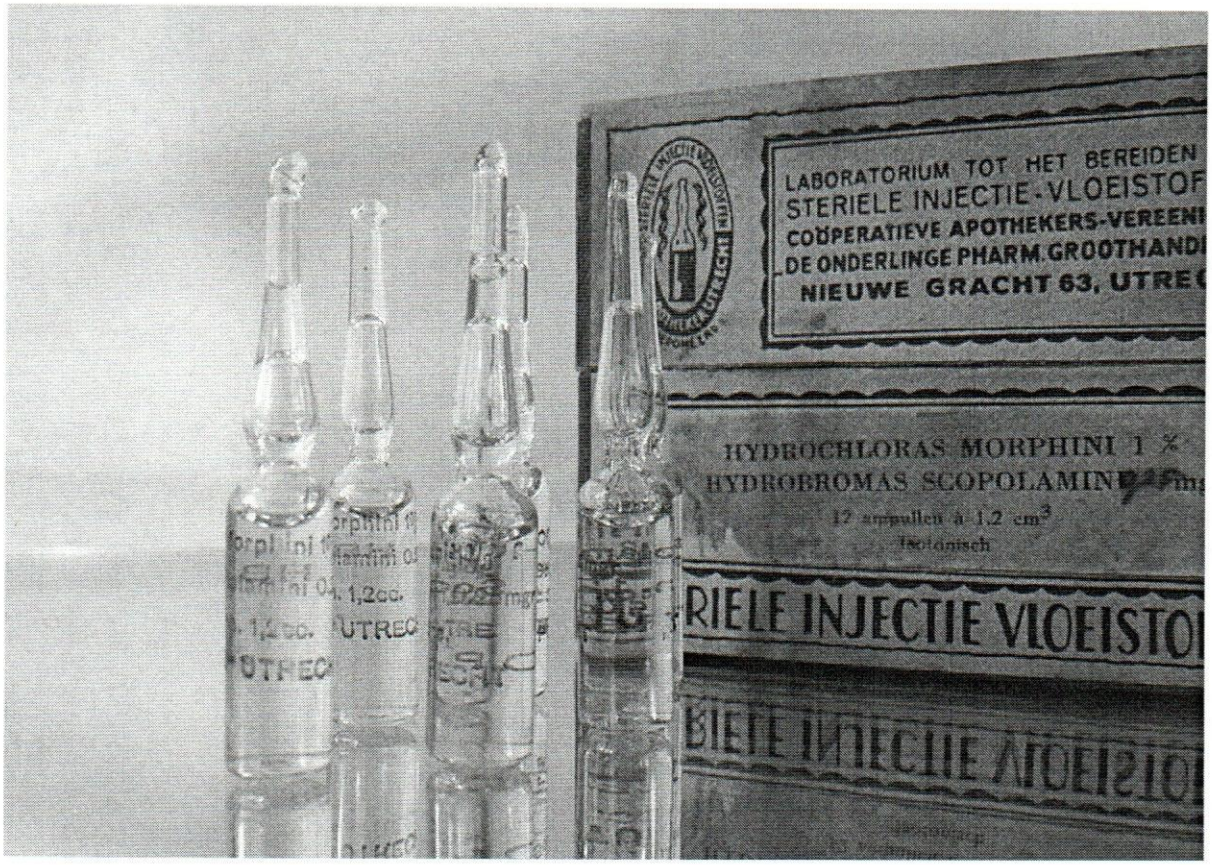
While pain is essential for survival and good health, unless you have masochistic tendencies, too much pain isn't a good thing. Especially if it persists. Millions of people live with chronic pain. And chronic pain, whether backache, joint pain or neuropathic pain (neuralgia) can make people's lives unbearable.

## Two centuries of morphine

Throughout recorded human history we have searched for substances to dull pain. The most powerful painkillers are the opioids. Morphine, derived from the opium poppy, is an opioid that has been

known to alchemists and medics for centuries. Morphine was one of the first ever medicines and has been available in a pure pharmacological form since 1817.

Morphine and synthetic opioids, such as codeine and fentanyl, bind to opioid receptors located on neurons in the spine and inhibit their activity. This prevents them signalling pain sensations to the brain. Some of our nerve cells, positioned in key places on the path along which pain signals travel, release opioid peptides (fragments of proteins) such as enkephalin. These enkephalins attach to opioid receptors and block pain signals reaching the brain. In the 1970s we discovered that opioids like morphine, codeine or fentanyl act as mimics of these naturally-occurring opioid peptides.




Morphine - effective but dangerous. Henk Albert de Klerk/Wikimedia Commons, CC BY-SA

So what has this all got to do with saliva? Well in 2006, a peptide named opiorphin was found in human saliva by researchers at Institut Pasteur International in Paris, France.

Opiorphin resembles enkephalin, but, rather than binding to opioid receptors to inhibit their activity, they prevent enkephalins from being broken down. So the amount of enkephalin – the body's natural painkiller – is increased and pain signals are blocked. When you experience pain, enkephalins are released and opiorphin boosts their action.

Opiorphin should only work in the places where enkephalin is being actively released and not affect other neural systems. So unlike conventional opioids it would only have a localised effect. In theory it would have the same effect on pain but without the wider unwanted side effects, such as addiction, tolerance with long-term use, and suppressed breathing.

## Opiorphin with a tweak

One problem is that opiorphin would be broken down in the digestive system or in the bloodstream so would not be able to get to particular sites in the body to block pain. So the researchers at Institut Pasteur worked with a company, Stragen, to create a modified version of opiorphin called STR-324, designed to increase its stability. STR-324 should be able to be taken orally or intravenously, though so far only an injectable form is being tested.

The team's most recent study looking at post-operative pain showed that STR-324, when injected, is effective at blocking pain in rats. The response compares well to morphine, with a lower painkilling effect than morphine.

Later this year, the company developing STR-324 will be testing the drug on humans for the first time. The current evidence suggests that STR-324 will work well for some types of pain, when injected.

The scientists will have a bigger challenge to show that the oral form of the drug is also effective.

A clinical trial for neuropathic pain (pain caused by problems with nerves themselves rather than through tissue damage) has been announced to begin in 2019. Neuropathic pain is common in people with poorly controlled diabetes and can occur following some viral infections. Neuropathic pain and other chronic pain syndromes are notoriously difficult to treat and are often resistant to conventional opioid drugs. If STR-324 is more effective for neuropathic pain that other opioids, it will be a significant new painkiller. That is a big if. The researchers have not yet modelled this type of pain in their experiments.

The main advantage of STR-324 over conventional opioids is that it is predicted not to cause respiratory depression, a reduction in breathing rate. This side effect is linked to fatalities with opioid use. While mostly this is unintentional drug overdose by people with heroin addiction, concerns about respiratory depression limit the medical use of opioids for pain management. The researchers will need to prove the advantages of STR-324 over other medicines. There is already a receptor-binding opioid, buprenorphine, where respiratory depression is less of significant clinical problem than for drugs like morphine and fentanyl.

The data for STR-324 is promising with a benefit that it works in a different way to theoretically provide a more targeted effect on pain systems than conventional opioids. The underlying scientific evidence that it will work in chronic pain, however, is light. The world does need new painkillers and, ultimately, it is only clinical trial data that will show whether STR-324 provides new hope for people living with chronic pain.

Painkillers Morphine