

RESEARCH ROUND-UP

Highlights from clinical trials on opioid research
By Neil Savage



BIOCHEMISTRY

Clue to what drives addiction

Rats that have too many copies of a microRNA in their brains might have a higher chance of becoming addicted to opioids.

MicroRNAs are short snippets of RNA molecules that don't create proteins themselves but can control how much genes are expressed. Scientists already knew that one, miR-9, was affected by giving mice either cocaine or morphine. Elena Chartoff and her colleagues at Harvard Medical School in Boston, Massachusetts, wondered whether overexpression of miR-9 would produce addictive behaviour in rats. The researchers used an adeno-associated virus, a common tool for gene therapy, to inject extra copies of miR-9 into the

nucleus accumbens — part of the brain's reward system that produces pleasure-giving dopamine in response to certain stimuli. They then taught that group of rats and a control group to press a lever to receive an injection of the opioid oxycodone.

At first, there was no difference between the two groups. But over several days, the rats with the extra copies of miR-9 began to press the lever more frequently and wait less time between injections. When the researchers looked at the animals' brains, they found that rats with extra miR-9 had increased expression of a dopamine receptor protein and decreased levels of a protein that suppresses gene expression at times that coincided with self-injection by the rats. The study shows that exposure to opioids leads to molecular changes in the brain that

increase drug consumption and might lead to addiction. *Int. J. Neuropsychoph.* 22, 383–393 (2019)

GENOMICS

Opioid addiction and genetics

Genes might play a part in making some people more vulnerable to opioid addiction than others. Matthew Randesi at the Rockefeller University in New York City is seeking clues as to why only 25–33% of people who take drugs such as heroin become addicted to them.

He and his colleagues at Rockefeller and in the Netherlands investigated whether there are genetic differences between people with an opioid addiction and those without. They took DNA samples from 281 people who

were being treated for heroin addiction, 163 people who had taken illicit opioids but had not become addicted, and 153 healthy volunteers who had never used illicit opioids. All study participants were of Dutch ancestry.

The researchers found 20 variants in 6 genes that seemed to be associated with opioid addiction. In particular, they found that a combination of three single-nucleotide changes in a specific gene had a significant association with such an addiction. The gene in question encodes the protein SLC18A2, also known as VMAT2, which packs neurotransmitters such as dopamine and serotonin into structures called vesicles, ready for secretion. The next step, the researchers say, will be to clarify how these gene variants contribute to the development of an addiction.

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Pharmacogenomics 20, 331–341 (2019).

DRUG MISUSE

Finding ways to prevent addiction

One way in which drug addiction spreads is when a drug user introduces a non-user to the act of injecting drugs — a phenomenon known as social communicability. But treating people who are already addicted to and injecting opioid drugs might make them less likely to pass on that addiction to others.

Dan Werb at the University of California, San Diego, and his colleagues tested the concept of ‘treatment as prevention’ for addiction by looking at data that had been gathered from injecting drug users in Vancouver, Canada, in 2014–17. Of 1,740 participants, 80 people said that they had within the past six months initiated new users by helping them to perform their first injection. Almost half of the study participants were being treated for addiction with opioid substitutes such as methadone or buprenorphine, and those who were actively participating in such therapy were 48% less likely to help another person to deliver their first injection. Researchers hope that this treatment-as-prevention approach will work well, in a similar way to how antiretroviral drugs have slowed the spread of HIV.

Drug Alcohol Depend. 197, 354–360 (2019)

ADDICTION

Blocking addiction in mice

Giving patients a drug that can block the function of opioid receptors before administering an opioid might help to prevent addiction, and could also reduce some of opioids’ unpleasant side effects.

Pao-Luh Tao at the National Defense Medical Center in Taipei and her colleagues

tested whether pretreating mice with the opioid-receptor blocker, or antagonist, naltrindole could alter the effects of oxycodone. Over the course of eight days, the team injected one group of mice with naltrindole, followed 30 minutes later by an injection of oxycodone. Another group received a saline injection first, and then oxycodone. A further group received naltrindole followed by a saline solution, and a control group received only the saline.

At the end of the study, the researchers stopped the treatments and looked for signs of opioid withdrawal. Mice that had been treated with the antagonist before receiving oxycodone showed fewer symptoms of withdrawal than did those who had been given only oxycodone, suggesting that they had become less physically dependent on the drug. A conditioning test found that the pretreated mice did not try to regain access to oxycodone after it was no longer being administered. Pretreatment also did not seem to decrease the opioid’s painkilling effects.

A common side effect of taking oxycodone is constipation. The pretreated mice, however, had much lower levels of constipation than did their untreated counterparts. Slowed breathing, an often lethal side effect of opioid overdose, was not affected by the use of naltrindole.

Eur. J. Pharmacol. 852, 265–273 (2019)

ANALGESICS

Discovering safer painkillers

A new opioid painkiller represents a lower risk for abuse and addiction than do existing drugs. The drug, NKTR-181, developed by Nektar Therapeutics in San Francisco, California, enters the central nervous system slowly and is also slow to activate opioid receptors,

which leads researchers to think that it might have a lower potential for abuse.

Conventionally, there has not been a satisfactory way to assess a drug for its abuse potential. But now, Analgesic Solutions, a company in Wayland, Massachusetts, that seeks to improve the design of clinical trials, has developed a system called MADDERS (Misuse, Abuse, and Diversion Drug Event Reporting System). MADDERS creates standardized definitions to help classify drug abuse during clinical trials.

To test the system, Ryan Lanier at Analgesic Solutions and his colleagues applied MADDERS to data from two

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consecutive clinical trials of NKTR-181 to determine how many ‘negative events’ had been reported.

The team looked at SUMMIT-07, a 12-week double-blind, randomized trial of the drug in people with lower-back pain, and SUMMIT-LTS, a 52-week open-label follow-on study. Of 1,189 participants in the SUMMIT-07 trial, 79 people (6.6%) experienced a total of 86 negative events. In the SUMMIT-LTS trial, 51 of the 683 participants (8%) experienced 59 negative events. The researchers described the number of events as low for this type of trial.

Most of the events that MADDERS identified could be categorized as symptoms of drug withdrawal, unintentional overuse or deliberate overuse to derive a therapeutic benefit. The researchers noted that the overall incidence of withdrawal symptoms for NKTR-181 was low. *Curr. Med. Res. Opin.* 35, 1513–1522 (2019)

DRUG DEVELOPMENT

Dual receptor activation

An opioid drug that targets two types of pain receptor shows strong pain-reduction effects but little potential for causing addiction in monkeys.

Stephen Husbands at the University of Bath, UK, and Mei-Chuan Ko at Wake Forest School of Medicine in Winston-Salem, North Carolina, and their colleagues tested a new analgesic drug called BU10038 in rhesus macaques (*Macaca mulatta*). The drug has promise as a painkiller because it is a partial activator of the μ -opioid receptor and the nociceptin receptor — both of which seem to play a part in pain reduction.

Monkeys were fitted with catheters that enabled them to self-administer BU10038. The researchers found that the drug delivered potent, long-lasting pain reduction by interacting with both types of receptor. However, it produced none of the behaviour-reinforcing effects that can lead to opioid addiction, even at a dose ten times that needed for treating pain.

The team also gave the drug to monkeys by injecting it into their spinal columns, a common way to provide pain relief for people undergoing surgery. When the potent opioid morphine is used, the procedure causes itching that can continue even after drug administration has been stopped. BU10038 given in this way produced no itching. And repeated administration of the drug, unlike morphine, did not seem to induce physical dependence or tolerance — factors that promote addiction.

BU10038 and other drugs that target both types of receptor might open the door to painkillers that do not lead to addiction, the researchers say. *Br. J. Anaesth.* 122, e146–e156 (2019)

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