RESEARCH ROUND-UP

Highlights from clinical trials on cannabis science
By Liam Drew

SPASTICITY

Cannabinoid hope for MND

A clinical trial of a cannabinoid oral spray that is used to treat people with multiple sclerosis (MS) suggests that the treatment could also ease the symptoms of motor neuron disease (MND).

The treatment targets spasticity, a condition caused by the permanent contraction of muscles, which impedes a person's movement. It is a prominent symptom of both MND and MS. In 2010, after a long history of people with MS using cannabis to self-medicate, a cannabis-based treatment to manage spasticity associated with MS was approved in the United Kingdom. Giancarlo Comi at Vita-Salute San Raffaele University in Milan, Italy, and his colleagues now suggest that this same cannabinoid preparation can ease spasticity in people with MND.

In a double-blind, randomized phase II trial, 30 people received a placebo and 29 people were given the cannabinoid spray — a solution containing roughly equal amounts of tetrahydrocannabinol (THC) and cannabidiol (CBD), the main psychoactive and non-psychoactive components, respectively, of cannabis. Participants spent two weeks finding a dosage with which they were happy, and then maintained that dose for four weeks. Spasticity was measured before and after treatment.

Whereas spasticity worsened slightly in the group that received a placebo, it improved in those who received the cannabinoid treatment. Of the participants who received cannabinoids, 55% reported feeling better, compared with only 13% of those given a placebo. The cannabinoids also decreased people's reported pain levels. Future studies might more finely distinguish the treatment's efficacy in two forms of MND: amyotrophic lateral sclerosis, in which spasticity varies in its prevalence and intensity, and the less common primary lateral sclerosis, which is often accompanied by severe spasticity.

Lancet Neurol. 18, **155–164 (2019)**

MENTAL HEALTH

Potent pot linked to psychosis

High-potency cannabis might carry greater risks to mental health than do less powerful strains. An international study led by Marta di Forti at King's College London suggests that people who use strains that contain large amounts of THC are more likely to develop psychosis — a condition in which a person's perception of reality is distorted.

The researchers surveyed 901 people with psychotic disorders, who had been admitted into psychiatric care at 10 sites in Europe and one in Brazil, about their present and past cannabis consumption. Their responses were then compared with those of 1,237 people without psychiatric diagnoses.

Consistent with previous studies, psychosis was three times more common in people who used cannabis daily than in people who had never used the drug. The researchers then grouped the participants according to whether they used strains of cannabis that are particularly rich in THC. Compared with non-users of cannabis, the odds of developing psychosis were more than twice as high for daily users of strains containing less than 10% THC. But using strains that contained more than 10% THC made the probability of developing psychosis almost five times higher than that of non-users.

Incidence of psychosis varied considerably between sites, and correlated with both the availability of high-potency cannabis and the number of people who used cannabis daily. These findings suggest that potency contributes considerably to regional variations in the prevalence of psychosis. By looking at where highly potent cannabis was most available, the researchers calculated that if daily use were accepted as causing psychosis, eliminating its use would reduce psychosis rates in London by 30% and in Amsterdam by 50%.

Lancet Psychiatry 6, **427–436 (2019)**

PAIN

Cannabinoids' analgesic promise

The case of a 66-year-old woman who feels only minimal pain might have revealed a new path to pain relief. Investigators think that inhibiting the breakdown of anandamide, a fatty-acid amide that interacts with cannabinoid receptors, could provide long-term pain relief.

The woman came to doctors' attention when, following an operation on her arthritic thumb, she required almost no pain relief. Her medical records revealed that after a hip replacement the year before she had similarly taken only paracetamol.

James Cox at University College London, Devjit Srivastava at Raigmore Hospital in Inverness, UK, and their colleagues surveyed the woman's genome in search of a genetic basis for her pain insensitivity. They discovered two genetic changes affecting an enzyme called fatty-acid amide hydrolase (FAAH). FAAH degrades a number of fatty-acid amides, including anandamide — an activator of the cannabinoid receptor CB_1.

One of the genetic changes was a common mutation that gives rise to a form of FAAH with low activity. The other was the deletion of a short region of DNA next to the gene encoding FAAH, which removed a gene that closely resembles FAAH. The researchers proposed that combining these changes would cause a person to exhibit low FAAH activity and, therefore, a build up of anandamide. The woman's blood samples confirmed this. The work suggests that an increased level of anandamide provides long-term suppression of pain signalling, and seems to clinically validate FAAH as a drug target — a development that might encourage more work on strategies aimed at dampening FAAH activity.

Br. J. Anaesth. 123, **e249–e253 (2019)**

IMMUNOLOGY

Inflammatory inhibition

A compound that targets the cannabinoid receptor CB_2 can powerfully suppress inflammation in humans. The drug candidate, ajulemic acid, has no psychotropic side effects, and strengthens the idea that CB_2 activators offer an alternative way of stopping inflammation.

CB_2 is almost absent from neurons in the central nervous system, so activating the receptor causes no psychotropic effects. It is, however, abundantly expressed on circulating immune cells, and researchers have known since the 1990s that activating CB_2 in rodents can suppress inflammation. Last year, Derek Gilroy at University College London and his colleagues, in collaboration with Corbus Pharmaceuticals in Norwood, Massachusetts, showed that ajulemic acid (developed by Corbus as Lenabasum) also dampened inflammation in humans.

"Altered brain function in people experiencing psychosis could be modified by a single dose of CBD."

Escherichia coli bacteria killed with ultraviolet light were injected into the skin of healthy volunteers to generate inflammation. Participants were then given a placebo, a widely used anti-inflammatory steroid or ajulemic acid. The researchers found that both the drug candidate and the steroid led to a dramatic decrease in the number of neutrophils that infiltrated the injection site, as well as a decrease in the production of certain pro-inflammatory lipid signalling molecules. But ajulemic acid also seemed to promote clearance of the bacteria and, at higher doses, to stimulate the body's natural mechanisms for resolving inflammation — effects that the steroid did not have.

Ajulemic acid is now undergoing phase II and phase III clinical trials in several rare autoimmune diseases, including lupus, but the compound might also be useful for more common inflammatory conditions such as arthritis.

Clin. Pharmacol. Ther. 104, **675–686 (2018)**

WEIGHT LOSS

Safer target for hunger blockers

Drugs that suppress appetite and promote weight loss by blocking the cannabinoid receptor CB_1 could be back on the menu, more than a decade after such a drug was withdrawn owing to its severe psychiatric side effects.

Rimonabant, approved in Europe for use as an anti-obesity drug in 2006 before being withdrawn two years later, targets CB_1 in the part of the brain that controls hunger. Blocking the receptor reduced appetite, but also interfered with other brain functions. Fresh findings suggest that drugs that block CB_1 found only in peripheral organs such as the liver could suppress hunger without inducing psychotropic side effects.

A study in mice, led by Jie Liu and George Kunos at the US National Institute on Alcohol Abuse and Alcoholism in Bethesda, Maryland, pinpoints two distinct pathways by which CB_1 in the liver affects metabolic processing. In mice fed a high-fat diet, CB_1 activation inhibited three interlinked intracellular signalling components in the liver, which was associated with excess glucose and insulin in the blood. Drugs that block CB_1 interfered with this pathway and helped to normalized glucose and insulin levels. The researchers also found that such drugs could reverse fat accumulation in the livers of mice fed a high-fat diet through a second pathway that increases fatty-acid oxidation.

The findings confirm a central role for CB_1 in regulating liver metabolism and put the clinical exploration of CB_1 blockers that are confined solely to peripheral organs on a firm mechanistic footing.

Hepatology 69, **1535–1548 (2019)**

MENTAL HEALTH

CBD might bring psychosis relief

The psychotic effects of cannabis are commonly attributed to its THC content. Conversely, CBD seems to have antipsychotic properties. A small clinical trial indicates that CBD can relieve changes in brain activity that are associated with psychosis.

To probe CBD's mechanism of action, Sagnik Bhattacharyya at King's College London and his colleagues used functional magnetic resonance imaging (fMRI) to see how the drug affected the brain activity of medication-free young adults who had sought psychiatric help and who were considered at high risk of developing psychosis.

Participants were given either a dose of CBD or a placebo. The two groups were then compared with healthy, age-matched individuals as they all performed a verbal learning task. Brain activity was recorded using fMRI at the baseline and during memory encoding and memory recall.

Compared with healthy people, the brains of those at high risk of psychosis showed diminished activation of the striatum during encoding, and of the medial temporal lobe and midbrain during recall. CBD seemed to partially reverse those changes: activation of the areas was still depressed compared with healthy individuals, but higher than that in people at high risk who were given a placebo.

The study suggests that altered brain function in people experiencing psychosis could be modified by a single dose of CBD, supporting the molecule's further development as an antipsychotic compound.

JAMA Psychiatry 75, **1107–1117 (2018)**

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