

Momentum grows for medical use of cannabis

An American girl whose life might have been saved by cannabis has inspired a surge of interest in cannabis-derived medications, which scientists say is long overdue. Chris McCall reports.

Charlotte Figi is now 7 years old and she has only just started school, but she is also internationally famous. Charlotte, from Colorado Springs, CO, USA, has the rare genetic condition Dravet syndrome and was not expected to live when her mother began treating her with cannabis in 2011. “We were dealing with 50 seizures a day, two an hour. She could not walk. She could not swallow”, her mother Paige Figi told *The Lancet*. “I started digging around. You are just watching your little baby girl die. I thought there has to be something to do for this poor kid.”

Since Paige started treating Charlotte with an laboratory-tested oil (given under the tongue, in a measured amount) derived from a specific, unusual strain of cannabis, the improvement has been remarkable. Publicity about the case has helped prompt a string of US states to legalise marijuana for medical purposes. Charlotte will never live an ordinary life, but she can talk with the aid of a computer and no longer needs a feeding tube.

The Figi family’s story has inspired thousands of other concerned parents, and has led to renewed pressure for laws on marijuana to be eased around the world. However, alongside the lobby for medical marijuana is a parallel lobby for legal recreational marijuana, and often the same people are pushing for both. Colorado, where the Figi family live, last year became the first US state to legalise the drug for recreational use. By next year, at least four US states will have done so. Last week, Australia announced that it would amend its drug laws to allow for cannabis to be legally grown for medical and scientific purposes.

Thorny issues

With more than 20 000 medical users in Canada, more than 20 000 in

Israel, and would-be users lining up around the world, medical marijuana looks set to stay. But doctors, pharmacologists, and other scientists say there are thorny issues over legal inconsistencies, lack of a solid evidence base, quality of the drug, and the fact that it is the only medicinal drug which can be smoked.

Perhaps the most thorny, however, and the most hotly debated, is the link between cannabis and schizophrenia, particularly in young users. Although the evidence is disputed, there is little doubt that at least some recreational users are at higher risk of developing psychotic illness.

“The Figi family’s story has inspired thousands of other concerned parents, and has led to renewed pressure for laws on marijuana to be eased around the world.”

Cannabis sativa originated in Asia and spread around the world, partly because as hemp it was a good source of strong fibre for ropes on sailing ships, very flexible, and resistant to rot. It has also historically been used as a medicine for numerous disorders. Cannabis is a dioecious plant, meaning male and female flowers are found on separate plants. It is around the female flowers that concentrations of the chemicals known as cannabinoids are found, leading smokers of marijuana to favour the female flowers, which have the greatest psychoactive properties. In nature, these substances seem to play a part in protecting the flowers from certain insects. They are only found in the cannabis plant.

In a parallel with the opium poppy, which gave the world morphine in the 19th century, cannabinoids interact with receptors found in the nervous

system of mammals. The science of this is well established and is not in dispute. However, the illegal status of cannabis has hindered research, says Jonathan Page, a plant biologist at the University of British Columbia, Canada, who has recently mapped the *C sativa* genome. “There is still a lot to be learned and to be discovered about this plant. Even getting samples of cannabis materials into a university lab is still very challenging”, he said.

The best known of the cannabinoids is tetrahydrocannabinol (THC), which is responsible for the high that smokers of cannabis seek. Over decades, marijuana growers have selectively bred plants greater and greater in concentrations of THC. Many modern plants contain several times more THC than in their ancestors. Pure THC is a clear oil and is a partial agonist of the receptors of the analogous human system. The second most abundant cannabinoid, cannabidiol, is less known. Referred to as CBD, it lacks psychoactive effects. In its pure form, it is a white powder, and as an antagonist, it has pharmacological effects that are largely opposite to THC.

The entire endogenous endocannabinoid system seems to be a



Charlotte Figi and her father at a cannabis greenhouse in Colorado Springs, CO, USA



Cristina Pedrazzini/Science Photo Library

modulator of the nervous system, operating in the synapses of nerves and regulating nervous activity. This property gives it wide-ranging effects, potentially making it a source for many clinically useful drugs. Apart from controlling seizures, potential and actual medical uses include treating Crohn's disease and other inflammatory conditions of the gut because of its anti-inflammatory properties, alleviating chronic pain in palliative care, preventing graft-versus-host disease in transplant patients, and even treating psychosis.

In Charlotte Figi's case, it was a strain of cannabis high in CBD and low in THC that controlled her seizures. Her mother Paige, who once did a pre-med course although she never trained as a doctor, says she discovered anecdotal accounts of cannabis being used to treat epilepsy dating back as far as the 18th century and devised her own informal tests with the help of a local marijuana grower in Colorado, to work out how much to give her daughter. Interestingly, plants high in THC made Charlotte's seizures worse.

Clinical trials

Israeli chemist Raphael Mechoulam, who discovered THC in 1964, says the flood of interest in cannabis-derived medications should have happened long ago. Evidence for effectiveness of CBD for seizures was obtained decades ago. "It is overdue. There is no doubt that cannabinoids from the plant and the equivalent molecules in the brain, which were discovered many years later, are of extreme interest", he said, citing as an example the use of cannabinoids for intractable pain in palliative care. "Pain is like an emotion and they seem to block the negative aspects of pain. People sometimes tell me 'I still feel the pain but I don't mind the pain'."

Mechoulam said his own past studies were also hampered by legal restrictions. In one case, police supplied seized Lebanese hashish for

research purposes, but the subsequent trials had to be done in South America, with a researcher in São Paulo taking a lead role.

Trials in severe paediatric epilepsy, chemotherapy-induced nausea and vomiting, and symptom relief in terminal illness have started this year in Australia. In Colorado, US\$9 million accumulated by the state as a result of medicinal cannabis sales over 15 years has been assigned to studies, including for inflammatory bowel disease, post-traumatic stress disorder, and sleep. British drug firm GW Pharmaceuticals is another organisation that is undertaking trials testing the use of cannabis derivatives in diabetes and schizophrenia among other disorders.

"How do you know which type of cannabis to use for a given condition? How do you know it is safe?"

Pot luck

How do you know which type of cannabis to use for a given condition? How do you know it is safe? Ryan Vandrey, a behavioural pharmacologist at Johns Hopkins University, MD, USA, says the answer is robust clinical trials and probably billions of dollars in research. At present, users of medicinal marijuana are running substantial risks, partly because of the lack of evidence. "People who smoke it can have a miserable time. That is going to be different from one person to the next and there is no way to predict ahead of time whether you are going to have a bad time. A lot of the side-effects are dose dependent", he said. "You don't have any of that science to really back up [medical use]. I would envisage that this is something that develops over decades."

The end result may be cannabis-derived drugs that go through a period on patent, during which they will be quite expensive, he says, and not quite the cheap cure-all that many

proponents imagine. In the end, though, doctors and pharmacists will be able to say with some confidence how these drugs work. Already some such drugs are on the market, such as Sativex (nabiximols), a mouth spray containing THC and CBD now marketed in some countries to relieve spasticity in multiple sclerosis.

Larry Wolk, a paediatrician who heads Colorado's public health division, says that initial data suggest that the negative effects from legalising marijuana for recreational use have not been as catastrophic as feared, although there has been a mild increase in emergency department admissions related to marijuana and at least one death related to edible marijuana.

Colorado's legalisation of recreational marijuana still involves some restrictions. Advertising is not permitted and only people older than 21 years can register as a recreational user, although younger people can potentially receive it for medical purposes. The people supplying both forms of marijuana are often the same. "If you are there for medical you turn to the left, if you are there for recreational you turn to the right", Wolk said.

Psychiatrist Michael Bostwick of the Mayo Clinic, MN, USA, is sceptical about medical marijuana, and says the current methods for prescribing cannabis in the USA involve some questionable practices. A US medical practitioner's licence is a federal licence and the federal government still lists cannabis and its main derivatives as schedule 1 drugs—meaning by definition that they have no medical use. Even if some states have legalised marijuana, the federal law has not changed. In reality, Bostwick says, prescriptions for cannabis in the USA are frequently not being issued directly by doctors, who would be taking a big personal risk. "They run the risk of losing their federal licence", he said.

Chris McCall