Are patients taking pot luck with cannabis?

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In July, Home Secretary Sajid Javid decided to reschedule cannabis-derived medicinal products to allow them to be legally prescribed by specialist clinicians. But while there is some scientific evidence supporting the use of cannabinoids in certain medical conditions, more research is needed to determine the full risks and benefits.

In 1872, Georg Ebers, a German Egyptologist, bought a papyrus wrapped in mummy cloths. The remarkably well-preserved roll, dating from around 1500 BC, catalogued the concoctions ancient Egyptian healers used to treat numerous diseases and symptoms, and transformed our understanding of ancient pharmacology.[1,2] Ancient Egyptians used cannabis, for example, as an enema, an anti-inflammatory ointment and, mixed with celery, as a topical treatment for eye disease.[3] In 1971, researchers reported that smoking marijuana lowers intraocular pressure. Today, cannabinoids remain an active area of research for glaucoma, although – in what becomes a mantra when discussing cannabinoid research – more studies are needed.[4]

Indeed, healers across much of the ancient world valued cannabis. Persians caring for the sick some 2700 years ago could choose from an armamentarium of more than 10,000 medicinal plants. Cannabis was among the most important.[5] In the sixth century AD, Chinese healers advocated cannabis for pain,[6] which remains an important indication today.

Then, in July this year, Home Secretary Sajid Javid decided to reschedule cannabis-derived medicinal products to allow their use on prescription. The Home Office said that by the autumn "senior clinicians will be able to prescribe the medicines to patients with an exceptional clinical need".

The Home Office's recent change of heart brings the UK's legal framework into line with numerous other countries, including Australia, Austria, Belgium, Canada, Denmark, Germany, Israel, Italy, the Netherlands, Norway, Portugal, Spain, Sweden and Switzerland, all of which have legalised medical cannabis. In the USA, cannabis remains illegal at federal level. But some 30 states and the District of Columbia now permit medical cannabis. Around 15 further states allow formulations that are high in cannabidiol and low in delta-9-tetrahydrocannabinol (THC).[7]

Edward Bednarczyk, Clinical Associate Professor of Pharmacy Practice at the University at Buffalo School of Pharmacy

and Pharmaceutical Sciences, attributes the change in the USA to a "drive to legalise recreational marijuana" and the hope that cannabis will provide "meaningful" medical benefits. "A major underpinning of both of these is the false assumption that cannabis is completely safe," he says. "The change offers a real-time example of how messages can become blurred and how willing both the public and healthcare providers are to suspend the existing process for drug approval."

Complex chemistry

Cannabis' long history of ritual, recreational and therapeutic use reflects the plant's marked biological activity. For many years, researchers focused on THC, the main psychoactive component of cannabis. But the cannabis plant contains more than 400 chemicals, including cannabidiol.[8]

Cannabidiol, which accounts for up to 40% of the plant extract, does not cause the euphoria induced by THC[8] and is legal in the UK. Indeed, cannabidiol-containing oils, food and drinks are increasing popular. But THC and cannabidiol only scratch the plant's pharmacological surface. Aileen Bryson, a spokesperson for the Royal Pharmaceutical Society (RPS), notes that at least 60 cannabinoids could have medicinal effects.

However, the plant's chemical composition varies between species of cannabis and depends on, for instance, preparation, growing conditions and harvesting. "The cannabis plant contains many different compounds with a wide spectrum of potential therapeutic effects, psychoactive actions, harms and adverse effects," says Ms Bryson. "So, prescribing the whole plant for medicinal purposes is not a safe option. There would be no consistency in the quality, the dosage, range of activity and unwanted side-effects. We always advocate the use of licensed products where it is possible to have this quality assurance."

Cannabinoids exert their wide spectrum of effects predominately by modulating the endocannabinoid system in, among other tissues, the nervous system, internal organs, connective tissues, glands and immune cells.[9] Indeed, research associates endocannabinoid deficiency or dysfunction to numerous diseases (see Table 1). Cannabinoids may also offer a novel approach to cancer treatment. In preclinical studies, for instance, cannabinoids inhibit proliferation, formation of new blood vessels, invasion and chemoresistance, induce apoptosis and autophagy, and enhance surveillance by the immune system.[10]

As you might expect from such a widely expressed and biologically influential system, endocannabinoid pharmacology is complex. Cannabinoid type 1 (CB_1) receptors are expressed throughout the CNS and in several other cells, such as adipocytes and hepatocytes, connective and musculoskeletal tissues, and the gonads.[9] The distribution in the brain suggests that CB_1 receptors modulate, among other biological functions, memory, emotion, pain and movement.[8]

The CNS also expresses CB_2 receptors. However, CB_2 receptors are present mainly in the spleen, tonsils, thymus and other tissues that produce and regulate immune cells.[8] Cannabidiol binds to CB_2 receptors, which seems to be one of several anti-inflammatory pathways affected by this cannabinoid. Cannabidiol also appears to stimulate synaptic plasticity and facilitate neurogenesis, which might explain the benefits on psychosis, anxiety and depression reported in some studies.[8]

CB_1 and CB_2 receptors bind endocannabinoid transmitters, such as anandamide (named after the Sanskrit word for bliss) and 2-arachidonoylglycerol (2-AG), both of which derive from phospholipids in cell membranes.[5,9] Anandamide, 2-AG, THC and cannabidiol also seem to bind to several other receptors including transient receptor potential ion channels, which also mediate the effects of capsaicin. In addition, 'entourage compounds' – such as oleamide – may prolong the effects of anandamide and 2-AG by competing for the metabolic enzyme.[9]

Hope in epilepsy

Given the endocannabinoid system's fundamental biological roles, it's perhaps not surprising that researchers tried cannabis-derived medicines for countless diseases. But the evidence seems particularly strong in some forms of epilepsy.

- Anorexia
- Chronic motion sickness
- Depression
- Failure to thrive in infants
- Fibromyalgia
- Huntington's disease
- Irritable bowel syndrome
- Migraine
- Multiple sclerosis
- Parkinson's disease
- Schizophrenia
- Seizure disorders

Table 1. Examples of diseases associated with endocannabinoid deficiency or dysfunction[9]

Again, the new studies build on an herbal heritage that dates back centuries. Arguably – depending on the translation – Akkadian and Sumerian healers used cannabis to relieve epilepsy in the second millennium BC.[11] But there's no doubt that the 20% to 30% of people who are resistant to conventional antiepileptic drugs require other therapeutic options.[12] Shelley Wagstaff, Advice and Information Services Manager at Epilepsy Action, notes that there is a particular need for new approaches to manage severe paediatric epilepsies.

Cannabidiol-based medicines are often effective in rare and treatment-resistant epilepsies, including Dravet and Lennox-Gastaut syndromes. The Food and Drug Administration (FDA) recently approved Epidiolex (purified cannabidiol) for Dravet and Lennox-Gastaut syndromes. The European Medicines Agency is currently reviewing Epidiolex, with a decision expected in early 2019.

A systematic review of six randomised controlled trials (RCTs) and 30 observational studies reported that adjuvant cannabidiol may reduce seizure frequency in paediatric-onset drug-resistant epilepsy. The average age of people involved in the studies was 16.1 years. In RCTs, cannabidiol increased the likelihood of at least a 50% reduction in seizure frequency by 74% compared to placebo. Patients taking cannabidiol were 6.17 times more likely to be seizure free than those taking placebo. In the observational studies, 48.5% of patients showed at least a 50% reduction in seizure frequency, while 8.5% were seizure free.[12]

Moreover, parents, patients and carers were 73% more likely say that the overall condition had improved in the cannabidiol group than with placebo. Indeed, 55.8% of patients in the observational studies reported enhanced quality of life when using cannabinoids. Mood, cognitive skills, alertness and sleep all improved.[12]

Nevertheless, Epilepsy Action welcomes the government's recent announcement that some cannabis-based treatments will be rescheduled by the autumn. "Rescheduling will allow for patients with exceptional clinical need, including some with severe and treatment-resistant epilepsies, to access cannabis-based medicines on prescription," Ms Wagstaff says. "This move will also allow for more rigorous and robust research into cannabis-based treatments without preventing access for those who need it most."

> "There is now a growing body of evidence from across the world that some cannabis derivatives, natural and synthetic, have potential for positive medicinal effects in several clinical conditions. We need to research this further, with proper clinical trials to improve patient care."
> Aileen Bryson, Royal Pharmaceutical Society

But there is still a need for further studies. "There is a serious lack of clinical evidence about the safety and efficacy of medical cannabis and THC in relation to the treatment of epilepsy," Ms Wagstaff says. "While there is anecdotal evidence to suggest [that] medical cannabis can help reduce seizures, there needs to be rigorous and robust research into understanding more about how effective and safe it is in treating epilepsy."

Ms Wagstaff adds that "very little scientific evidence" supports cannabis oil containing THC and cannabidiol in the management of epilepsy. "Treatments containing high concentrations of THC are unlicensed," she says. "There is evidence that THC can make seizures worse and cause other serious side-effects, such as psychosis and other mental health problems, particularly in children and adolescents."

In addition, cannabidiol is typically added to other antiepileptic medicines. "But very little is known about how cannabidiol interacts with these other medicines," Ms Wagstaff says. "We would like to see cannabidiol become an additional treatment option for clinicians treating people with challenging epilepsies. However, we know it is not a silver bullet and is unlikely to be effective for everyone with epilepsy."

Even more mixed evidence

The evidence base might be incomplete in epilepsy, but it's even more shaky in many other indications. Whiting and colleagues systematically reviewed 79 RCTs (encompassing 6462 people) that assessed cannabinoids in a variety of conditions. In most studies, cannabinoids improved symptoms, although the differences did not always reach statistical significance. Overall, the meta-analysis found moderate or low-quality evidence supporting cannabinoids for chronic pain, spasticity, nausea and vomiting due to chemotherapy, sleep disorders, Tourette's syndrome and weight gain in people with HIV. For example, compared with placebo, cannabinoids were associated with a significant increase in the proportion of patients who showed complete resolution of nausea and vomiting (20% and 47% respectively; odds ratio [OR] 3.82). The mean reduction in the Ashworth spasticity scale was also statistically significant.[13]

Chronic, poorly controlled pain is one of the main reasons for people taking cannabinoids, especially in the light of growing concerns regarding opioid analgesics. Whiting and colleagues reported that cannabinoids increased the proportion of people who reported at least a 30% reduction in chronic pain – most commonly, neuropathic pain, cancer pain and diabetic peripheral neuropathy – compared to placebo (37% and 31% respectively), although this just missed statistical significance. The average pain reduction was a statistically significant 0.46 difference on a 0 to 10-point scale.[13] In a more recent meta-analysis of 104 RCTs encompassing 9958 people, 29.0% of those taking cannabinoids reported at least a 30% reduction in pain compared to 25.9% of the placebo group. The reduction in pain intensity was 3mm greater on a 100mm visual analogue scale in patients taking cannabinoids.[14]

On the other hand, Australian researchers followed 1514 people who had been living with chronic non-cancer pain for a median of 10 years. The patients had been prescribed strong opioids for a median of four years. The median oral morphine equivalent dose was 75mg daily. During the four-year follow-up, 24% of participants had used cannabis for pain. Compared with those who did not try cannabis, users had a 14–17% (depending on frequency of use) greater pain severity score at the four-year follow up, 14–21% greater pain interference score, 2–3% lower pain self-efficacy scores and 7–10% greater generalised anxiety disorder severity scores. "No evidence" emerged that cannabis influenced opioid use.[15]

The limitations of the evidence base might account for the mixed results. For example, most studies evaluated by Whiting and colleagues assessed nausea and vomiting caused by chemotherapy, chronic pain or spasticity. Far less evidence supported the other indications. In addition, many studies showed methodological weaknesses, such as enrolling small numbers, failing to appropriately handle withdrawals and reporting selected outcomes.[13]

Professor Bednarczyk adds that adverse events have become somewhat

neglected in all the excitement around cannabis' medical potential. Certainly, adverse events are common. Based on three RCTs in people with epilepsy, patients who received cannabidiol showed a statistically significant 24% increase in the risk of experiencing any adverse event compared with placebo. People receiving cannabidiol were, for instance, almost three times more likely to experience drowsiness (relative risk [RR] 2.53) and diarrhoea (RR 2.63) and six times more likely to report fatigue (RR 5.80) and changes in appetite (RR 5.46) than those receiving placebo.[12] In the meta-analysis of pain studies, 81.2% of people taking cannabinoids reported adverse events compared to 66.2% of those receiving placebo.[14] "The adverse effects of cannabis are real and often ignored," Professor Bednarczyk says.

Moving forward

While medical cannabis seems to be a potential treatment for some diseases, much more research is needed to determine the risks and benefits. "Many people are dancing around the big question," Professor Bednarczyk says. "Is a particular cannabinoid better or at least equivalent to existing therapy? There is plenty of anecdotal evidence for cannabinoids, but that's not the typical standard that we use for assessing a drug. At the end of the day, comparator studies need to be done."

In the meantime, the Home Office has announced that by the autumn "senior clinicians will be able to prescribe [cannabis-derived medicinal products] to patients with an exceptional clinical need". Only products that meet a clear definition being prepared by the Department for Health and Social Care (DHSC) and the Medicines and Healthcare products Regulatory Agency (MHRA) will be rescheduled and prescribed.

The change follows two reviews commissioned by the government. Initially, the Chief Medical Advisor, Professor Dame Sally Davies, "concluded that there is evidence that medicinal cannabis has therapeutic benefits". The Advisory Council on the Misuse of Drugs (ACMD) then considered the appropriate schedule for cannabis-derived medicinal products by balancing "harms and public health requirements".

The ACMD recommended that products that meet the clear definition should be in Schedule 2 of the Misuse of Drugs Regulations 2001. The DHSC and the Home Office will develop "frameworks and clinical guidelines to ensure that cannabis-derived medicinal products can be prescribed safely to patients but cannot be traded illicitly".

"The RPS supports a change in legislation moving cannabis from Schedule 1 of the Misuse of Drugs Regulations 2001 into Schedule 2," says Ms Bryson.

"This will allow research in the UK to be carried out much more easily, including clinical trials and prescribing of products licensed in other countries where appropriate. Schedule 1 contains drugs known to have little or no therapeutic value and there is now a growing body of evidence from across the world that some cannabis derivatives, natural and synthetic, have potential for positive medicinal effects in several clinical conditions. We need to research this further, with proper clinical trials to improve patient care."

In the meantime, clinicians can apply to the independent expert panel on behalf of patients with exceptional clinical needs. According to the current regulations, the clinician making the application "would be expected to show that there is no other lawful medicinal product (whether licensed or not) that would meet the specific need of the patient".

A grown-up discussion

But will medical use lead to the legalisation of recreational marijuana? Cannabis is certainly popular. The Crime Survey for England and Wales reported that 6.6% of people aged between 16 and 59 years used cannabis during 2016/17. About three times more people used cannabis than the next most popular drug, powder cocaine (2.3%). And 29.6% of people admitted using cannabis at some time. Non-medical sale of cannabis is legal in Uruguay[7] and, from October 2018, Canada.[16] Professor Bednarczyk believes there is a "high probability" that medical use will ultimately end in the legalisation of recreational use in the USA.

"We need to have a 'grown-up' discussion about marijuana," Professor Bednarczyk says. "A good comparator recreational agent might be ethanol. Ethanol is widely used, but it carries a certain societal cost that includes dependence, and a variety of health-related costs that much of the world chooses to accept. Recreational marijuana also leads to dependence in about 10% of users, pulmonary problems, exposure to carcinogens and impairment when driving. If we are willing to consider and accept these costs, then so be it, but we should at least have that discussion."

It will probably be some time before we have a 'grown-up' discussion in the UK. "Medicinal use is quite a separate issue from recreational use, so we must not conflate the two," says Ms Bryson. "It does not follow that any changes to the scheduling will have any impact on the issues and arguments around recreational use, which comes with many harmful effects, particularly on mental health."

Certainly, there seems to be little political appetite to change the law. The Home Office stresses that the "announcement does not pave the way towards legalising cannabis for recreational use". In March this year, market research company Populus interviewed 109 MPs. The survey found that only 12% 'strongly' or 'somewhat' supported the legalisation of recreational cannabis. Another 16% were undecided.

Until the recent announcement, the UK's position over 'cannabis-derived medicinal products' seemed increasingly out of touch with public opinion, legislation in comparable countries and the (albeit less than ideal) evidence base. The change brings new hope to people with debilitating and distressing conditions, many of whom have run out of conventional options. And the change should encourage new and much needed research.

"There are many unanswered questions around the potential medicinal use of cannabis and its derivatives. [However,] ultimately, we have the possibility of new treatments for some very debilitating conditions," Ms Bryson concludes. "But it takes more than 10 years to bring a new medicine to the market. So, we need more research to start now."

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Declaration of interests

Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. He has no shares or financial interests relevant to this article.

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