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Cite this as: *BMJ* 2022;376:n3114
http://dx.doi.org/10.1136/bmj.n3114
Published: 26 January 2022

ESSAY

Why doctors have a moral imperative to prescribe and support medical cannabis—an essay by David Nutt

Medical cannabis has been legal to prescribe since 2018—yet just a handful of prescriptions have been made in three years. The reasons: stigma, fear, and an entrenched resistance in the medical profession that is harming patients, writes David Nutt

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The field of medicine developed empirically with doctors doing what they could to help reduce the suffering and improve the health of their patients. Medicines were what doctors gave patients to assist this process. Medical cannabis presents a novel challenge to current medical practice—many patients reporting large benefits from self-medicating with illicitly sourced products would dearly like to have them prescribed on the NHS but are unable to do so.

Cannabis has been classed as a medicine in the United Kingdom since November 2018 (box 1). The decision to make it available as a medicine was precipitated by the case of Alfie Dingley, a boy with severe epilepsy who nearly died after returning from Canada when his medical cannabis was confiscated by custom's officers. Sally Davies, then the chief medical officer, recommended the government move plant based cannabis extracts from schedule 1 to schedule 2 of the 1971 Misuse of Drugs Act, at the request of the home secretary.[2]

Box 1: Medical cannabis in the UK

National Institute for Health and Care Excellence guidelines recommend four licenced cannabis based medical products that can be prescribed in the UK[1]:

- Two tetrahydrocannabinol (THC) based medicines: dronabinol, licensed for appetite loss in AIDS and as an antiemetic in chemotherapy, and nabilone, licensed for nausea in people receiving chemotherapy
- Sativex, a combined THC and cannabidiol medicine for muscle spasticity in multiple sclerosis
- Epidyolex (99.8% cannabidiol with less than 0.1% THC) for two rare childhood epilepsies (Lennox-Gastaut and Dravets syndrome)

A multitude of other unlicensed cannabis based products (such as oils and herbal cannabis) are produced to good manufacturing practices standard and can now be prescribed.

In the subsequent three years, however, only a handful of prescriptions have been made on the NHS. So most of the estimated 1.4 million patients using it are doing so with illicit supplies—with all the legal and product dose and quality risks that entails.[3] Others are paying hundreds or even thousands of pounds a month for their medicine from private specialists.[4]

One reason for this lack of prescriptions is a condition of the legislative change stating that only specialists can initiate prescribing, not GPs (although a GP can continue prescribing after treatment has been started). And although there are GPs who would prescribe cannabis if they could, there remain others who dare not. So the 2018 legislation might have looked like a solution to the problem of children such as Alfie Dingley, who require cannabis to stay alive, but in practice it was not.

A 2021 GP survey found that 24% of respondents wanted to be allowed to prescribe.[5] What is holding the UK back? The reasons are multifactorial and complex.[6] But one thing stands out: the resistance of the medical profession to endorse this new treatment paradigm.

Do no harm

Perhaps the most egregious example of medical resistance came from the current chief medical officer, Chris Whitty, in a statement to the Health Select Committee in 2019.[7] When asked why medical cannabis was not being rolled out, he replied, "We have to conduct research in such a way that we avoid another thalidomide tragedy."

Another more clinically immediate example is the refusal of the British Paediatric Neurology Association (BPNA) to recommend NHS prescription of medical cannabis to children with severe treatment refractory epilepsy, in whom it has shown unprecedented efficacy and allowed many children to stop taking multiple ineffective epilepsy drugs. The first case series of 10 patients has been replicated in a further 10 patients and published in *BMJ Paediatrics Open*.[8] A bayesian analysis of treatment efficacy of medical cannabis in these 20 patients predicts that any future patient has over a 90% chance of a good response (L Phillips, personal communication, 2021).

The BPNA's reason for refusal is that there is "no evidence of efficacy," despite each of these 20 patients having shown a response, sometimes a 100 times reduction in seizure frequency. In many of these children, the medical cannabis worked despite Epidyolex, the only authorised cannabinoid medicine for epilepsy, having failed. In contrast to the BPNA guidance stating that prescribing medical cannabis is probably not in the best interests of children,[9] the above case study series clearly and consistently shows that, for these children, medical cannabis treatment is in their best interests.

The hostility of the BPNA to medical cannabis culminated in their reporting to the General Medical Council (GMC) a doctor who was legally prescribing full spectrum cannabis for childhood epilepsy with good anticonvulsant effect.[10] The GMC exonerated the doctor in question and emphasised that his action was fully compliant with current guidance. The BPNA's own expert said that the association was not acting in the best interests of the children. This bullying action by the BPNA has been discomforting and stressful to the families and the doctor.

Another remarkable example of the therapeutic benefits of medical cannabis is the case of Lucy Stafford, a 21 year old with Ehlers-Danlos syndrome.[11] She had been in hospital almost permanently since experiencing joint dislocations after her first surgery aged 10, then she had 19 further operations throughout her teenage years, becoming bedbound at 17 and on heavy doses of opiates including fentanyl, despite which the pain was severe and disabling. She developed gastroparesis from the combination of Ehlers-Danlos syndrome and opiates, which required intravenous nutrition from the central line that then led to sepsis with six admissions to intensive care.

Her pain specialist suggested medical cannabis as a last resort for the extreme pain from a permanently dislocated jaw. The prescription was turned down for NHS funding with a letter saying that cannabis was unlikely to work and that there was a one in four chance she would end up with psychosis. Stafford and her mother went to Amsterdam and sourced medical cannabis. Slowly but surely, her jaw began to unlock. She was able to reduce her opiates and other medications. She has since become able to walk unaided, and she started a degree in neuroscience at Sussex University in September.

Stafford's private prescription for cannabis initially cost £1450 a month. Now, thanks to the Project Twenty21 initiative, this is down to £450 a month. This initiative is a collaboration between the charity Drug Science (which I founded and of which I am trustee) and six registered producers. Project Twenty21 facilitates access to medical cannabis at cost price after patients have been seen and received a diagnosis from a specialist. This represents a massive saving to the NHS—when Stafford was on a feeding tube, her medication alone cost over £250 a day, and the hospital room was very much more; overall more than £100 000 a year. Despite these huge savings, her local Cambridge hospital trust refuses to allow her doctor to prescribe cannabis for her on the grounds of "lack of evidence of efficacy." One wonders what evidence could ever convince them that medical cannabis works?

Stigma and fear

The UK position reflects many different factors but standing out is a deep—hopefully subconscious—stigma in UK doctors, hospital pharmacists, and clinical commissioning groups against medicines that have not been developed in the now conventional manner of drug industry driven randomised controlled trials (RCTs) with subsequent NICE approval.

Let us examine the arguments made against prescribing medical cannabis. One is that medical cannabis might be harmful because of a lack of traditional preclinical safety testing. As Chris Whitty indicated, the fear is that without this testing another thalidomide tragedy is possible. This argument has many flaws. First, preclinical testing would not have detected the risks of thalidomide as it doesn't cause malformations in rodents.[12] Moreover, both THC and cannabidiol have been through preclinical toxicology studies and proved not to be teratogenic.[13] More importantly, cannabis has been used as a medicine for millennia without any signs of fetal harm; with tens of millions of recreational users in the US, Canada, Holland, and Spain, among other countries, many of whom are women, no such issues have been reported.

Similarly, some detractors say that RCTs are needed before any conclusions on efficacy can be proved. This is a common misunderstanding of the nature of medical evidence. Although care should be taken when comparing clinical responses without head-to-head comparisons (owing to differences in study design, population, and so on),[14] Michael Rawlins, former head of the Medicines and Healthcare Products Regulatory Agency and NICE, pointed out in 2008 that RCTs are not the apex of treatment trials. He argued that there were many other forms of evidence that can equally inform medical practice. These include patient reported outcomes, real world evidence, effectiveness trials, and case series.[15]

RCTs are expensive and, with new medicines, largely conducted by for-profit drug companies. Very few of the cannabis responsive conditions reported by patients are being studied. Reasons for this include difficulties in patenting whole plant extracts given their complex mixture of minor cannabinoids[16] and reluctance of the UK to license plant based medicines. The traditional RCT approach was used for cannabidiol in two forms of childhood epilepsy (Lennox-Gastaut and Dravet syndromes) by GW Pharmaceuticals. It took 20 years to complete, and the company's application for NHS use was then turned down by NICE on grounds of cost efficacy (though this has now been reversed). Unsurprisingly, other companies have seen this as a serious barrier to moving into this field. If the same requirement for RCT evidence had been applied to penicillin, it might never have been developed as a medicine.

RCTs are also not representative of patient groups because patients with comorbidities are usually excluded. Project Twenty21 data indicate that most of the patients included in the initiative have various comorbidities, including major depression and other brain disorders such as insomnias.[17]

Another commonly expressed concern, as stated to Lucy Stafford, is the risk of dependence and psychosis. Again, international data show that this doesn't occur to any substantial extent—an audit of 100 000 Canadians found two cases each of psychosis and schizophrenia and similarly few examples of dependence.[18] Though the risk of cannabis causing an enduring psychosis is still controversial,[19] we know that the most risky products have a high concentration of THC without the protective effects of cannabidiol—for example, skunk,[20] used by young people to achieve intoxication. The risk is markedly mitigated when cannabis is prescribed under medical supervision. A detailed explanation of the reasons for this, with safer use guidelines, are given in Schlag and colleagues' recent review.[17] Additionally, open communication between doctor and patient about both benefits and risks of medical cannabis, as well as continuous pharmacovigilance, will ensure patient safety.

Some doctors may have the paternalistic attitude that patients should defer to medical experts rather than discover their own solutions. A recent qualitative study of parents and carers using medical cannabis to treat their child's epilepsy supports this conclusion, showing the challenging relationship between the doctor (who often lacks specific expertise on medical cannabis) and the parent (who had to develop expertise to be able to treat their child's condition).[21]

The profession's ignorance of cannabis and the endocannabinoid system coupled with decades of cannabis prohibition justified by the denial of its medical value must also play a part. Chris Whitty's

quote indicates a desire to close off discussion rather than have a frank debate about the issues.

Arguments for

We now have a great deal of real world evidence for medical cannabis as the result of patients seeking better treatments for their chronic conditions. Patients are using cannabis medicines for many different reasons,[22] often with singular benefit over previous treatments. To insist that they continue to source cannabis from the illicit market, with its known issues of quality and content, until a commercial company does an appropriate trial is perverse, patronising, and inhumane.

Real world evidence can provide data for specific patients that RCT results in other patients cannot. As every doctor knows, the reality of medicine is that for every patient every new treatment is an n=1 experiment. Individual patient outcome measures are the gold standard of the value of the treatment. The data on severe childhood epilepsies prove this point.

As well as having specific medical benefits, the use of medical cannabis in other countries has had substantial collateral benefits. One particularly encouraging finding—especially given the continuing opioid epidemic in the US—is the possibility of reducing the use of opioid analgesics in patients with chronic pain.[23 24] Recent patient reported outcomes show that medical cannabis is regularly used as a substitution drug,[25] with the most common medications substituted being opioids, anxiolytics or benzodiazepines,[26] and antidepressants.[27] Substitution frequency is higher for patients using medical cannabis to treat comorbidities (such as the triad of pain, anxiety, and depression) than for those with a single condition. This impact is now seen at a population level—in US states where medical and recreational cannabis are widely used, deaths from opioid overdose have fallen.[28]

Moral imperative

The controversy over medical cannabis seems to be specific to the UK. In many cases it has challenged one of the core elements of medical practice: the doctor-patient relationship. No doctor disputes that good medical practice requires including patients in decision making about their medical plans and to value their reported outcomes and wishes. Legare and colleagues review evidence collected from many studies since the 1970s that highlight the importance of patients as decision makers in their own treatment. This evidence shows that treatment outcomes are better when doctors and patients are in agreement and that it is important to offer holistic and humane care. For many physicians and patients, this is a paradigm shift in the patient-doctor relationship, and adoption has been slow so far.[29] This approach has been part of the development of shared decision making, which evolved from a growing awareness of the limits of medical interventions and of the lack of control over decisions about one's own care.[30] GMC guidelines on decision making and consent emphasise that "shared decision making and consent are fundamental to good medical practice."[31]

There is a moral argument for the medical profession to give up its resistance. Denying patients access to a treatment that could help them or their children until a drug company conducts trials to gain a licence conflicts with a fundamental principle of medicine—that doctors should use the current best knowledge to assist their patients. And drug companies might never bother to study that indication.

Overall, the reasons given by medical leaders and NHS authorities such as NICE for denying the value of medical cannabis seem anachronistic and intellectually dishonest. They go against the medical requirement of doing one's best for one's patient with the extent of knowledge at the time. And they add to NHS costs by encouraging continued use of other ineffective treatments. It is time the UK accepted—indeed embraced—medical cannabis as a major medical advance and allowed all doctors including GPs to prescribe.

Biography

David Nutt is a psychiatrist and professor of neuropsychopharmacology at Imperial College London. He trained at Cambridge, Guys Hospital, and Oxford University in the UK, and the National Institutes of Health in the US. His research focuses on how drugs work in the brain and the mechanisms underpinning psychiatric disorders, particularly addiction and depression. He has published over 700 research papers, 36 books, and 8 government reports. He founded the charity Drug Science in 2009 and won the John Maddox prize for standing up for science in 2013.

Provenance and peer review: Commissioned; externally peer reviewed.

Competing interests: I have read and understood BMJ policy on declaration of interests and declare the following interests: I sit on the advisory boards of several research and drug companies, which have no connection to medical cannabis. I have been paid to speak by several drug companies that do not produce medical cannabis products. I founded and chair the scientific committee of the charity Drug Science, which is funded by individual donations, a grant from Open Society Foundations, and book sales. Drug Science receives an unrestricted educational grant from a consortium of medical cannabis companies. My role at Drug Science is unpaid and I do not stand to gain from the wider availability and prescription of medical cannabis.

Anne Katrin Schlag contributed to the revision and editing of the manuscript.

1 National Institute for Health and Care Excellence. Cannabis based medicinal products. NICE guidelines [NG144] 2019. https://www.nice.org.uk/guidance/ng144

2 Davis S. Cannabis scheduling review: the therapeutic and medicinal benefits of cannabis based products. A review of recent evidence. 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/722010/CMO_Report_Cannabis_Products_Web_Accessible.pdf

3 Couch D. Left behind: the scale of illegal cannabis use for medicinal intent in the UK. Centre for Medicinal Cannabis. 2020. https://www.thecmcuk.org/left-behind-the-scale-of-illegal-cannabis-use-for-medicinal-intent-in-the-uk

4 Zafar R, Schlag AK, Nutt D. Ending the pain of children with severe epilepsy? An audit of the impact of medical cannabis in ten patients. *Drug Sci Policy Law* 2020;6:1-6doi: 10.1177/2050324520974487.

5 Primary Care Cannabis Network. UK GP attitudes towards medical cannabis survey 2021. https://primarycarecannabisnetwork.com/wp-content/uploads/2021/07/Uk-GP-Attitudes-towards-medical-cannabis-2021-FINAL.pdf

6 Nutt D, Bazire S, Phillips LD, Schlag AK. So near yet so far: why won't the UK prescribe medical cannabis? *BMJ Open* 2020;10:e038687. . doi: 10.1136/bmjopen-2020-038687 pmid: 32958492

7 Whitty C, Health and Social Care Committee. Drugs policy: medicinal cannabis. Mar 2019. https://www.parliamentlive.tv/Event/Index/954fe835-ca5f-4fed-9415-eeba45fe18ea

8 Zafar R, Schlag AK, Phillips LD, etal. Medical cannabis for severe treatment resistant epilepsy in children. *BMJ Paediatr Open* 2021;5:e001234. doi: 10.1136/bmjpo-2021-001234 .

9 British Paediatric Neurology Association. Guidance on the use of cannabis-based products for medicinal use in children and young people with epilepsy. 2021 https://bpna.org.uk/_common/show_unpro_doc.php?doc=BPNACBPMsguidanceupdate-dOct2021_8b7f3bbc1af32e3ef188b6274100591f.pdf

10 Gibbons K. Inquiry after doctor "gives baby cannabis." *Times* 30 Mar 2021. https://www.thetimes.co.uk/article/inquiry-after-doctor-gives-baby-cannabis-d2s2hb3zj

11 Dar S. Treating pain related to Ehlers-Danlos syndrome with medical cannabis. *BMJ Case Rep* 2021;14:e242568. doi: 10.1136/bcr-2021-242568 pmid: 34301703

12 Kazuki Y, Akita M, Kobayashi K, etal. Thalidomide-induced limb abnormalities in a humanized CYP3A mouse model. *Sci Rep* 2016;6:21419. doi: 10.1038/srep21419 pmid: 26903378

13 Valim Brigante TA, Abe FR, Zuardi AW, Hallak JEC, Crippa JAS, de Oliveira DP. Cannabidiol did not induce teratogenicity or neurotoxicity in exposed zebrafish embryos. *Chem Biol Interact* 2018;291:81-6. doi: 10.1016/j.cbi.2018.06.008 pmid: 29902416

14 Schlag AK, Hindocha C, Zafar R, Nutt DJ, Curran HV. Cannabis based medicines and cannabis dependence: A critical review of issues and evidence. *J Psychopharmacol* 2021;35:773-85. doi: 10.1177/0269881120986393 pmid: 33593117

15 Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. *Lancet* 2008;372:2152-61. doi: 10.1016/S0140-6736(08)61930-3 pmid: 19101391

16 Russo EB. The case for the entourage effect and conventional breeding of clinical cannabis: No "strain," no gain. *Front Plant Sci* 2019;9:1969. doi: 10.3389/fpls.2018.01969 pmid: 30687364

17 Sakal C, Lynskey M, Schlag AK, Nutt DJ. Developing a real-world evidence base for prescribed cannabis in the United Kingdom: preliminary findings from Project Twenty21. *Psychopharmacology (Berl)* 2021; doi: 10.1007/s00213-021-05855-2 pmid: 33970291

18 Health Canada. Canada vigilance adverse reactions database. 2021. https://cvp-pcv.hc-sc.gc.ca/arq-rei/index-eng.jsp

19 Wainberg M, Jacobs GR, di Forti M, Tripathy SJ. Cannabis, schizophrenia genetic risk, and psychotic experiences: a cross-sectional study of 109,308 participants from the UK Biobank. *Transl Psychiatry* 2021;11:211. doi: 10.1038/s41398-021-01330-w pmid: 33837184

20 Di Forti M, Quattrone D, Freeman TP, etalEU-GEI WP2 Group. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry* 2019;6:427-36. doi: 10.1016/S2215-0366(19)30048-3 pmid: 30902669

21 Schlag AK, Zafar R, Nutt D. Medical cannabis and epilepsy in the UK—a qualitative analysis of the carers' perspective: "We're asking for quality of life for our children." *Drug Sci Policy Law* 2021;7. doi: 10.1177/20503245211034930.

22 Schlag AK, O'Sullivan SE, Zafar RR, Nutt DJ. Current controversies in medical cannabis: Recent developments in human clinical applications and potential therapeutics. *Neuropharmacology* 2021;191:108586. doi: 10.1016/j.neuropharm.2021.108586 pmid: 33940011

23 MacCallum CA, Eadie L, Barr AM, Boivin M, Lu S. Practical strategies using medical cannabis to reduce harms associated with long term opioid use in chronic pain. *Front Pharmacol* 2021;12:633168. doi: 10.3389/fphar.2021.633168 pmid: 33995035

24 Okusanya BO, Asaolu IO, Ehiri JE, Kimaru LJ, Okechukwu A, Rosales C. Medical cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review. *Syst Rev* 2020;9:167. doi: 10.1186/s13643-020-01425-3 pmid: 32723354

25 Gittins R, Sessa B. Can prescribed medical cannabis use reduce the use of other more harmful drugs?*Drug Sci Policy Law* 2020; doi: 10.1177/2050324519900067.

26 Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int J Drug Policy* 2017;42:30-5. doi: 10.1016/j.drugpo.2017.01.011 pmid: 28189912

27 Lucas P, Baron EP, Jikomes N. Medical cannabis patterns of use and substitution for opioids and other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduct J* 2019;16:9. doi: 10.1186/s12954-019-0278-6 pmid: 30691503

28 Hsu G, Kovács B. Association between county level cannabis dispensary counts and opioid related mortality rates in the United States: panel data study. *BMJ* 2021;372:m4957. doi: 10.1136/bmj.m4957 pmid: 33504472

29 Légaré F, Härter M, Stiggelbout AM, et al. Choosing treatments and the role of shared decision-making. In: Anell A, Nolte E, Merkur S, eds. Achieving person-centred health systems: evidence, strategies and challenges. Cambridge University Press, 2020; 283-316.

30 Illich I. *Limits to medicine. Medical nemesis: the expropriation of health* Marion Boyards Publishers, 1975.

31 General Medical Council. Decision making and consent. 2020. https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/decision-making-and-consent