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So near yet so far – why won't the UK prescribe medical cannabis?

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So near yet so far – why won't the UK prescribe medical cannabis?

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Abstract
Although cannabis-based plant medicines (CBPMs) are now legal in the UK, it is still challenging for patients to gain access, and only very few NHS prescriptions have been written to date. This paper attempts to make sense of why the UK lags behind so many other countries which also have legalized medical cannabis. From consulting with parents and patients, prescribers, pharmacists and decision makers it seems that there are a series of distinct barriers to prescribing that need to be overcome in order to improve patient access to medical cannabis in the UK. These include concerns about the perceived lack of scientific evidence. To alleviate these concerns, we highlight the importance of patient-centred approaches including patient-reported outcomes, pharmacoepidemiology, and n=1 trials, which can contribute to the development of the evidence base for medical cannabis. We hope that this paper will help policy makers and prescribers understand the challenges to prescribing and so help them develop approaches to overcome the current unsatisfactory situation.

Article Summary: Strengths and weaknesses

- There are a series of distinct barriers to prescribing medical cannabis that need to be overcome in order to improve patient access in the UK.
- Concerns about the perceived lack of RCT evidence are misplaced as many patient-centred approaches including patient-reported outcomes, pharmacoepidemiology, and n=1 trials can be applied.
- Thousands of UK patients self-medicating with CBPMs and the international data base evidence suggest these new medical products offer a significant advance in treatment for many in whom current medicines are either ineffective or poorly tolerated.
- We hope that this paper will help policy makers and prescribers understand the challenges to prescribing and so help them develop approaches to overcome the current unsatisfactory situation.

Introduction
In Nov 2018 when the UK made cannabis-based plant medicines (CBPMs) legal most people assumed these would immediately be made available to patients, but they were wrong. In the year since almost no NHS prescriptions have been issued [1] and less than a hundred have been made available from private providers at a cost of at least £1000 a month [2]. For these reasons, some parents of children with severe epilepsy continue to go overseas to get their children access to the only treatment which has proven to be effective for their condition. Moreover, the vast majority of

the estimated 1.4 million medical cannabis users [3] source from the black market with its problems of illegality, unknown quality, content and provenance. Given the substantial evidence of utility of CBPMs in many disorders as identified in the US National Academy of Sciences review in 2017 [4] this failure of delivery in the UK seems odd and, to many, inexcusable.

Concerns about perceived lack of evidence

Statements such as “insufficient evidence of efficacy” or “it is too dangerous” are common and used even in the face of strong personal evidence from patients that CBPMs work and, in many cases, can be lifechanging and well tolerated. Many doctors fail to include the evidence of the patient-lived experience and cite the lack of placebo-controlled trials in every possible indication for their hesitation to prescribe. Whilst tens of thousands of individual patient reports of the therapeutic value of CBPMs as in the Canadian and NY State data bases [5] do not equate to the so-called gold-standard double-blind RCT level of proof, they are highly suggestive of a pattern of evidence which should be taken seriously rather than summarily dismissed.

The major criticism of the lack of placebo-controlled trials is misplaced. Prescribers often mistakenly state that without these they cannot prescribe. However, there are over 50 medicines or indications that have been licensed by FDA and/or EMA between 1999 and 2014 without randomised controlled trial data [6].

Moreover, the ex-head of NICE and the MHRA, Sir Michael Rawlins, challenged this RCT preconception in the 2008 Harvean Oration, highlighting that *“randomised controlled trials (RCTs), long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of "hierarchies" of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base.*[7]

Placebo controlled double-blind trials are clearly a very important element of medicine where their primary role is to provide evidence for companies to get a marketing authorisation. Such trials are done in tightly selected patient groups that are not representative of the average patient who often has many different medical comorbidities. Therefore, even when such trials are positive, they are only suggestive of efficacy in the wider patient groups and other approaches such as effectiveness trials or clinical audits are required to properly estimate real-world value to individual patients.

Of these new approaches, patient-reported outcomes [PROs] are probably the most significant development. These have received immense investment from the USA NIH and many new scales have been developed for this purpose. PRO measures are now required as elements of outcome measures for clinical trials funded by the NIH in the USA [https://commonfund.nih.gov/promis/index]. PROs put more emphasis on the patient’s life and wellbeing and have been shown to be more sensitive to the effects of medical cannabis than traditional symptom-based measures. For example, a large recent naturalistic German study on pain syndromes using PROs found adding a CBPM very significantly improved outcomes in patients with neuropathic pain [8]. Other recent papers showing real-world benefits from CBPMs using patient reports have been reported in Parkinson's disease [9] and autism [10]. NICE has developed a cadre of expert patients to advise them of the patients perspective [https://www.scie-socialcareonline.org.uk/the-expert-patients-rogramme/r/a1CG0000000GNbcMAG] although it is not apparent if this includes a patient with experience of medical cannabis. Progress in this direction has led to the setting up of a special centre in Cambridge for patient-led research in the clinical trials unit: https://www.cuh.nhs.uk/clinical-trials/cambridge-clinical-trials-unit-cctu/patient-led-research-hub.

Pharmacoepidemiology and, specifically, observational research is another recent patient centred approach to study the effectiveness of real-world medication [11]. Advantages include the availability of large patient samples, coverage of under-researched subpopulations in their naturalistic conditions and lower costs than RCTs [12]. The limitation of the non-randomised nature of treatment selection can be addressed by including comparison groups, or through the triangulation of multiple analytical approaches to improve confidence in inferred causal relationships.

With many clinicians demanding better and faster evidence to inform their decisions around prescribing CBPMs, these newer approaches offer potential solutions to the lack of RCTs. Indeed, in line with rapid developments in data resources and analytical techniques, many guidelines are now beginning to include evidence from robust observational pharmacoepidemiological studies alongside RCTs [12].

But even more important are the n=1 trials, for these are **the core** of medical practice since every time a medicine is prescribed an n=1 experiment is being conducted. In some patients the experiment works and in others it fails, the patient either does not respond or the adverse effects outweigh the therapeutic benefit. One might therefore expect that doctors would welcome patients who have conducted successful self-treatment with cannabis since it is almost certain that prescribing medical cannabis to these will work, providing a therapeutic win for both patient and prescriber.

The resurrection of CBPMs following its banning by the UN Conventions is directly attributable to n=1 trials conducted in children with intractable epilepsy. The first was Charlotte Web in the USA that inspired UK parents of children with similar epilepsies notably Alfie Dingley and Billy Caldwell. These children were facing death and/or brain damage from multiple seizures resistant to licensed treatments and CBPMs restored them to close to normality and also allowed them to come of other medicines. In the case of Billy, the proof of therapeutic efficacy was dangerously established by the confiscation of his medical cannabis by UK customs which led to a life-threating episode of status epilepticus requiring admission to intensive care. The public outcry over such callous treatment by the UK government was the immediate cause of the rescheduling of medical cannabis in November 2018.

In scientific terms Billy was the subject of an A-B-A design, one of the most powerful methodologies for examining a medical intervention. The UK government accepted that in these cases CBPMs worked. So why would any prescriber resist similar claims in their patients, particularly if they had seen their own previously prescribed treatments fail? In such cases to deny a patient a CBPM simply because they are using an “illegally” sourced preparation is illogical and could be construed as being unethical. Germany took this view when deciding to make medical cannabis available. The GMC guidance on good medical practice makes it clear that all registered doctors must take into account and respect patients’ views and experience.

Scientific support for ABA trials is well established in educational, behavioural and psychological assessment but less so in medical research [13]. An ABA(B) trial design is well-suited for determining whether medical cannabis is efficacious. Bayesian analysis can also combine separate ABA(B) results from different populations of patients, such as cannabis and non-cannabis users, stratified as suggested by experts whose experience has identified possible confounding variables [14]. This approach is known as multi-level regression and post-stratification (MRP) [15].

What are the reasons for this resistance?

One source of this resistance is that because CBPMs are patient-driven, to welcome them would be an admission that the patients are more knowledgeable than the doctor. Despite over a decade of

demands by the DHSC for patients to have a say in medical practice in the UK, there has been little progress. In this debate it is usually forgotten that cannabis was a licensed medicine in the UK before 1971. So why does the government not just re-issue the license that applied then? Phenergan and chloral hydrate have continued to be available in the UK since that time despite no double-blind clinical trial data and chloral is sometimes used as an anti-epilepsy treatment in the children with epilepsy who are denied CBMPs!

Another factor is the "not invented here" syndrome. UK prescribers often say they only trust data collected here; an attitude justified by our high-quality health technology assessment processes especially NICE. However, to ignore data from other countries in a field as complicated as medical cannabis likely distorts the truth. Medical cannabis has been available for over a decade in many states in the USA and there are over 400,000 patients on the Canadian Health data base. These data should be interrogated as a way to accelerated clinically-relevant information to potential prescribers as the Health Secretary Matt Hancock stated in July 2019 [16].

This statement calls into question the current DHSC rule that medical cannabis must be considered a "Special". The challenges of Specials to prescribers are not trivial and include:

1. Organisational bureaucracy and the subsequent delay of prescribing, approval and supply
2. Transferring a patient between one sector and another, especially where e.g. primary care will not continue prescribing of a superficially expensive special or unlicensed product
3. Local secondary and primary care services having different rules and guidance, particularly about prescribing unlicensed medicines
4. Responsibility for prescribing - a licensed product's manufacturer is accountable for any untold harm if the product is used within the license, but with an unlicensed product or Special the **prescriber** assumes responsibility for any harm that occurs, unless it can be directly attributed to a defect in the actual product.

These complexities do give some support to doctors' perception of prescribing as too difficult. Moreover, the DHSC has made cannabis a special "special" as prescribing requires a special pink pad that has to be ordered. Why such constraints are required is unclear given the established safety of cannabis medicines, but they are problematic for the prescriber and likely deter use.
Most UK doctors have no experience of medical cannabis and comments like "I don't know what to prescribe" are often heard. Though understandable they reflect poorly on a profession which generally welcomes engaging with new therapeutics; until medical cannabis came along prescribers were rarely fearful of new therapeutics. Moreover, new is not really a credible term given the decade of CBMPs use in USA, Canada and The Netherlands. The 1998 House of Lords report on medical cannabis provided clear evidence on efficacy and value of medical cannabis [17]. Both d9THC [e.g. as nabilone] and a mixture of d9THC and cannabidiol [as Sativex] have been licensed medicines in the UK for over a decade. The decision to move cannabis to Schedule 2 was made on the basis that there was adequate data that it was a medicine [18]. It is true that there is little in the way of teaching on medical cannabis in the undergrad or postgrad medical curricula but there are several free on-line teaching courses on medical cannabis to remedy this shortcoming, including one run by our charity DrugScienceorg.uk.

Perhaps one reason for resistance to CBPMs is that for nearly 50 years the medical profession focused of the risks of cannabis with extreme claims of harms, including male sterility, lung cancer and schizophrenia. Though these have now been largely debunked and were generally the result of recreational rather than prescribed medical use, many practitioners may not know this. Even if they do, there can be significant concern in prescribing a drug that has been vilified for decades as toxic. Here education is the solution.

The pharmacy perspective

Pharmacists (especially at Clinical Commissioning Group level) and medical prescribing advisors also play a significant role, often through Area Prescribing Committees (APCs). Pharmacy advisors tend to think of themselves as guardians of the public purse in relation to medicines prescribing. Their default position is usually to resist the cost implications of new medicines by blocking approval to local prescribing lists. Here the resistance is often derived from a misplaced focus of prescription costs with the cost benefits of saving in other medicines and interventions being ignored; e.g. medical cannabis can reduce the use of strong opioids [19, 20], and lower prescription costs [21].

We suggest that APCs should give CBPMs a fair chance by:

- Agreeing with the relevant consultants e.g. pain or neurology clinics, a specified number of patients each year
- Factor in the costs of the alternatives e.g. opioid overuse (due to lack of efficacy for many pains), benzodiazepines and pregabalin/gabapentin over- or self-medication
- Take genuine notice of testimonies from patients, who will not be diverting CBPMs because they need it
- Remember that generic substitution of CBPMs is not an option either as all products have proportions of THCs and CBD and will give different actions
- Remember that many CBPM products do not have sufficient d9THC in them to make patients 'stoned'
- Ensure better training locally

Conclusions

The many thousands of UK patients self-medicating with CBPMs and the international data base evidence suggest these new medical products offer a significant advance in treatment for many in whom current medicines are either ineffective or poorly tolerated. They also offer the potential of significant cost savings to the NHS in terms of reduced hospital stays and less prescribing of other medicines particularly opioids for chronic pain. The failure of the medical and pharmacy professions to embrace CBPMs despite their being made "legal" 12 months ago is a great worry to patients and will already likely have led to preventable deaths from conditions such as epilepsy. We hope that this paper will help policy makers and prescribers understand the challenges to prescribing and so help them develop approaches to overcome the current highly unsatisfactory situation.

Contributorship statement

Prof David Nutt is guarantor and developed the initial manuscript. Prof Larry Phillips and Dr Anne Schlag developed the section on concerns about perceived lack of evidence. Prof Steve Bazire wrote the pharmacy perspective. All authors reviewed the manuscript and agreed on the final submission.

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Ethical approval was not required.

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Dr Schlag is a paid researcher for Drug Science a charity that receives unrestricted educational donations from several sources including some companies that manufacture or distribute medical cannabis products. The others declare no conflicts.

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Article Summary: Strengths and weaknesses

- There are a series of distinct barriers to prescribing medical cannabis that need to be overcome in order to improve patient access in the UK.
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With many clinicians demanding better and faster evidence to inform their decisions around prescribing CBPMs, these newer approaches offer potential solutions to the lack of RCTs. Indeed, in line with rapid developments in data resources and analytical techniques, many guidelines are now beginning to include evidence from robust observational pharmacoepidemiological studies alongside RCTs [13].

But even more important are the n=1 trials, for these are **the core** of medical practice since every time a medicine is prescribed an n=1 experiment is being conducted. In some patients the experiment works and in others it fails, the patient either does not respond or the adverse effects outweigh the therapeutic benefit. One might therefore expect that doctors would welcome patients who have conducted successful self-treatment with cannabis since it is almost certain that prescribing medical cannabis to these will work, providing a therapeutic win for both patient and prescriber.

The resurrection of CBPMs following its banning by the UN Conventions is directly attributable to n=1 trials conducted in children with intractable epilepsy. The first patient was Charlotte Web in the USA who inspired UK parents of children with similar epilepsies notably Alfie Dingley and Billy Caldwell. These children were facing death and/or brain damage from multiple seizures resistant to licensed treatments and CBPMs restored them to close to normality and also allowed them to come of other medicines. In the case of Billy, the proof of therapeutic efficacy was dangerously established by the confiscation of his medical cannabis by UK customs which led to a life-threating episode of status epilepticus requiring admission to intensive care. The public outcry over such callous treatment by the UK government was the immediate cause of the rescheduling of medical cannabis in November 2018.

In scientific terms Billy was the subject of an A-B-A design, one of the most powerful methodologies for examining a medical intervention. The UK government accepted that in these cases CBPMs worked. So why would any prescriber resist similar claims in their patients, particularly if they had seen their own previously prescribed treatments fail? In such cases to deny a patient a CBPM simply because they are using an “illegally” sourced preparation is illogical and could be construed as being unethical. Germany took this view when deciding to make medical cannabis available. The GMC guidance on good medical practice makes it clear that all registered doctors must take into account and respect patients’ views and experience.

Scientific support for ABA trials is well established in educational, behavioural and psychological assessment but less so in medical research [14, 15]. An ABA(B) trial design is well-suited for determining whether medical cannabis is efficacious. Bayesian analysis can also combine separate

ABA(B) results from different populations of patients, such as cannabis and non-cannabis users, stratified as suggested by experts whose experience has identified possible confounding variables [16]. This approach is known as multi-level regression and post-stratification (MRP) [17].

What are the reasons for this resistance?

One source of this resistance is that because CBPMs are patient-driven, to welcome them would be an admission that the patients are more knowledgeable than the doctor. Despite over a decade of demands by the DHSC for patients to have a say in medical practice in the UK, there has been little progress. In this debate it is usually forgotten that cannabis was a licensed medicine in the UK before 1971. So why does the government not just re-issue the license that applied then? Phenergan and chloral hydrate have continued to be available in the UK since that time despite no double-blind clinical trial data and chloral is sometimes used as an anti-epilepsy treatment in the children with epilepsy who are denied CBMPs!

Another factor is the "not invented here" syndrome. UK prescribers often say they only trust data collected here; an attitude justified by our high-quality health technology assessment processes especially NICE. However, to ignore data from other countries in a field as complicated as medical cannabis likely distorts the truth. Medical cannabis has been available for over a decade in many states in the USA and there are nearly 20,000 patients on the Minnesota database, providing detailed data on various conditions and PROs since 2015. These data should be interrogated and formally published as a way to accelerate clinically-relevant information to potential prescribers as the Health Secretary Matt Hancock stated in July 2019 [18].

This statement calls into question the current DHSC rule that medical cannabis must be considered a "Special". The challenges of Specials to prescribers are not trivial and include:

1. Organisational bureaucracy and the subsequent delay of prescribing, approval and supply
2. Transferring a patient between one sector and another, especially where e.g. primary care will not continue prescribing of a superficially expensive special or unlicensed product
3. Local secondary and primary care services having different rules and guidance, particularly about prescribing unlicensed medicines
4. Responsibility for prescribing - a licensed product's manufacturer is accountable for any untold harm if the product is used within the license, but with an unlicensed product or Special the **prescriber** assumes responsibility for any harm that occurs, unless it can be directly attributed to a defect in the actual product.

These complexities do give some support to doctors' perception of prescribing as too difficult. Moreover, the DHSC has made cannabis a special "special" as prescribing requires a special pink pad that has to be ordered. Why such constraints are required is unclear given the established safety of cannabis medicines, but they are problematic for the prescriber and likely deter use.

Most UK doctors have no experience of medical cannabis and comments like "I don't know what to prescribe" are often heard. Though understandable they reflect poorly on a profession which generally welcomes engaging with new therapeutics; until medical cannabis came along prescribers were rarely fearful of new therapeutics. Moreover, new is not really a credible term given the decade of CBMPs use in USA, Canada and The Netherlands, and its subsequent publications on the practical considerations in medical cannabis administration and dosing [19]. The 1998 House of Lords report on medical cannabis provided clear evidence on efficacy and value of medical cannabis [20]. Both delta-9-THC [e.g. as nabilone] and a mixture of delta-9-THC and cannabidiol [as Sativex, made from whole plant extracts] have been licensed medicines in the UK for over a decade. The decision to move cannabis to Schedule 2 was made on the basis that there was adequate data that it was a medicine [21]. Whilst there is little in the way of teaching on medical cannabis in the

undergrad or postgrad medical curricula, the past couple of years have seen an increasing amount of medical cannabis educational programmes of varying standards. Especially for clinicians it is essential to be able to find non-biased educational programmes, highlighting the need for accredited training to be made available. Drug Science is currently offering free on-line teaching courses on medical cannabis and is also working on the development of accredited courses together with the Society for the Study of Addiction.

Perhaps one reason for resistance to CBPMs is that for nearly 50 years the medical profession focused of the risks of cannabis with extreme claims of harms, including male sterility, lung cancer and schizophrenia. Though these have now been largely debunked and were generally the result of recreational rather than prescribed medical use, many practitioners may not know this. Even if they do, there can be significant concern in prescribing a drug that has been vilified for decades as toxic. Here education is the solution.

Furthermore, patients self-medicating are often using the same illicitly sourced products as recreational users, making differentiation between uses challenging for clinicians. For both patient and doctor, access to fully regulated products could ensure a known dose and a quality and content that can actually be monitored.

The pharmacy perspective

Pharmacists (especially at Clinical Commissioning Group level) and medical prescribing advisors also play a significant role, often through Area Prescribing Committees (APCs). Pharmacy advisors tend to think of themselves as guardians of the public purse in relation to medicines prescribing. Their default position is usually to resist the cost implications of new medicines by blocking approval to local prescribing lists. Here the resistance is often derived from a misplaced focus of prescription costs with the cost benefits of saving in other medicines and interventions being ignored; e.g. medical cannabis can reduce the use of strong opioids [22, 23], and lower prescription costs [24].

We suggest that APCs should give CBPMs a fair chance by:

- Ensure better training locally
- Agreeing with the relevant consultants e.g. pain or neurology clinics, a specified number of patients each year
- Factor in the costs of the alternatives e.g. opioid overuse (due to lack of efficacy for many pains), benzodiazepines and pregabalin/gabapentin over- or self-medication
- Take genuine notice of testimonies from patients, who will not be diverting CBPMs because they need it
- Remember that generic substitution of CBPMs is challenging as all products have different ratios of THC and CBD and may give different actions
- Remember that there are many CBMPs with low THC or absent of THC. Also, the common routes of ingestion (i.e. oral oil/capsule) make it unlikely for patients to have immediate intoxication effects.
- In order to clarify cost implications of prescribing CBMPs, it is essential to conduct a full health economic analysis. Quality cost savings analyses are lacking at present and will be important for governments to enable active changes.

Conclusions

The many thousands of UK patients self-medicating with non-regulated CBPMs and the international data base evidence suggest these new medical products offer a significant advance in treatment for many in whom current medicines are either ineffective or poorly tolerated. They also offer the potential of significant cost savings to the NHS in terms of reduced hospital stays and less prescribing

of other medicines particularly opioids for chronic pain. The failure of the medical and pharmacy professions to embrace CBPMs despite their being made "legal" over 18 months ago is a great worry to patients and will already likely have led to preventable deaths from conditions such as epilepsy. We hope that this paper will help policy makers and prescribers understand the challenges to prescribing and so help them develop approaches to overcome the current highly unsatisfactory situation.

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Prof David Nutt is guarantor and developed the initial manuscript. Prof Lawrence D Phillips and Dr Anne K Schlag developed the section on concerns about perceived lack of evidence, and the importance of n=1 trials. Dr Steve Bazire wrote the pharmacy perspective, and the suggested guidance for Area Prescribing Committees. All authors reviewed the manuscript and agreed on the final submission.

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