KNOWN UNKNOWNS OF MEDICAL CANNABIS

Understanding the Limitations and Innovations of Medical Cannabis Prescribing in the UK

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volteface

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Foreword - Dr Steve Hajioff

The use of cannabis for medicinal purposes remains a contentious issue. While there is a growing body of evidence that certain cannabinoids and products extracted from cannabis plants can be beneficial for some conditions, and despite the law now permitting the prescribing of cannabis-based prescription medicines (CBPMs) over and above those that have been licensed, relatively few patients have received cannabis products on prescription in the United Kingdom (UK).

In the four years since the rescheduling of cannabis-based products for medical use in 2018, developments have largely been led either by cannabis enthusiasts—be they prescribers or patients—or by challenging and heart-wrenching paediatric cases where cannabis is a treatment of last resort. One of the consequential problems to arise is that, by definition, supporters and unusually tragic cases do not represent the overwhelming majority of mainstream thought and care, and therefore the solutions they generate may not dovetail with the broader community and the services they deliver and utilise. It is for this very reason that the approach to this report is so important and timely. By focusing on the perceptions, understanding and concerns of a range of practising clinicians across specialties, it highlights that clinicians and systems are not unreasonable barriers to accessing care, but rather thoughtful and reasoned actors whose practice is governed by fundamental principles. That a medicinal product should be supported by robust evidence on the efficacy prior to being widely offered to patients should not be a contentious matter, nor should the requirement for evidence on the product's associated safety and consistency.

Over many decades, medicine has developed mechanisms for assessing whether a potential treatment helps or harms patients that are not only tried and tested, but also trusted by the overwhelming majority of prescribers. Any deviation from this approach thus requires robust justification, due to the potential for risk to patients under treatment. It is therefore unsurprising that the interviewed clinicians overwhelmingly sought the same type and standard of research applied to CBPMs as applicable for other medicines. It is also to be expected that they would favour the use of products supported by evidence in a given indication over those that are not. But these things need to be clearly stated, and this report does precisely that; moving the debate away from enthusiasts seeking to passionately effect change, towards a clinical community realising evidence-based improvements to extend the range of cannabis-based products available for prescription.

Note to the reader: The conclusions and recommendations contained herein do not necessarily reflect the views and opinions of the individuals and organisations that have contributed to this report.

Executive Summary

Known Unknowns represents a dive deep into the perceptions, concerns and hopes of UK clinicians for medical cannabis, which although being legal since 2018 still sits on the fringes of the UK healthcare system with prescribing remaining low. This report recognises that in order to move forward, the industry faces challenges, and for cannabis to become mainstream as a treatment, a number of concerns that currently exist amongst clinicians must be addressed.

Clinicians are in many respects the gatekeepers to expanding medical cannabis access in the UK, having at their disposal a framework that facilitates prescribing. Nevertheless, despite the existence of this framework, only an estimated 0.25% of clinicians who are able to prescribe CBPMs currently do so.

The purpose of this report is therefore to provide clinicians with an opportunity to better understand and examine the barriers they face in regards to medical cannabis, and to offer solutions for how these can best be overcome.

Volteface conducted interviews with 41 clinicians specialising in pain, psychiatry, gastroenterology, rheumatology and neurology in order to understand their perceptions towards medical cannabis.

A qualitative thematic analysis revealed three key themes that contribute to clinicians' hesitations—evidence, governance and the perceived uniqueness of medical cannabis—with their concerns summarised as follows.

Evidence:

The perceived insufficiency of medical cannabis evidence was a major barrier for the clinicians' willingness to prescribe, with a range of opinions expressed in terms of the quality of evidence. Although randomised controlled trials (RCTs) are the gold standard, some clinicians noted the need for other types of evidence and research. Most agreed that the real-world evidence was biased due to the influence of the prevailing preconceptions in the cannabis community that tend to amplify the perceived benefits of the medicine rather than determining its true efficacy, thus leading many of the clinicians to view the medical cannabis sector with scepticism. They also voiced concerns regarding the risks, side effects, interactions and long-term impacts of prescribing CBPMs, which extended to the link between cannabis and psychosis, particularly with a large portion of patients already suffering comorbid psychological conditions.

Governance:

The vast majority of the clinicians reported that they lacked support, guidance and education on the practicalities of prescribing medical cannabis. Many were unclear on how to legally source medical cannabis, or what steps would be required in order to prescribe it to a patient. Although multidisciplinary support would increase their confidence, discomfort arose through the risk of being exposed to criticism and legal ramifications. This lack of structured education on the topic was exemplified by the broad range of perspectives on the existence and validity of the evidence base, even among clinicians within the same specialty. Overall, the bureaucracy and costs involved in prescribing medical cannabis appeared to dissuade clinicians from doing so.

Executive Summary

Uniqueness of Cannabis:

While the clinicians strongly voiced that cannabis should be treated like any other medicine, this poses a significant challenge given its unique nature. The modes of administration represented a concern for many clinicians, while due to the complexity of cannabis as a medicine, the clinicians tended to cite a lack of sufficient knowledge in order to justify a decision to prescribe.

Most of the clinicians expressed a willingness to learn more about prescribing, particularly due to the urgent unmet need for novel drugs given treatment-resistance to medication amongst patients. There was also discussion surrounding cannabis providing a promising alternative to prescribing opioids as a potential harm-reduction strategy. The illicit status of cannabis renders it subject to stigma, which was a concern frequently raised in the context of clinicians being broadly conservative by default, due to factors including their duty of care towards their patients, as well as the nature of the medical model they train under and work within.

On a practical level, according to the clinicians the prohibition and the current scheduling of cannabis creates additional barriers, where they raised concerns regarding the existence of an illicit market alongside the legal medical counterpart that can drive patients to self-medicate illegally, due to the narrow list of licensed indications for prescribing.

Ideologically, some clinicians spoke about how the prevailing illegal status of cannabis contributes to the stigma and hesitancy of prescribing in the medical community. Concern and hesitancy surrounded clinicians prescribing cannabis for recreational as opposed to legitimate medical purposes. Many did not want to develop a reputation as a cannabis prescriber, which might lead them to see more patients requesting prescriptions without a legitimate need.

Recommendations

This report makes the following recommendations to address the aforementioned challenges that are limiting medical cannabis prescribing:

1. Mainstreaming cannabis prescribing in clinicians' daily practice:

As detailed by the clinicians in the research, there is a hesitancy to join cannabis clinics as nowhere else in the medical system are there single drug clinics. To address the hesitancy and resistance that exists in the medical community, we should seek innovative means to promote prescribing through creating new opportunities to prescribe outside of the cannabis clinics, while engineering an infrastructure to empower clinicians to prescribe cannabis in normal clinical settings.

2. Open up communities of practice for clinicians to access medical cannabis information:

The disparate perceptions over the quantity, quality and acceptance of evidence indicates a need to streamline knowledge in the medical community. As the vast majority of clinicians revealed that they lack support in terms of the practicalities of the prescribing process, it is important to ensure that the necessary information is available to clinicians through multiple channels in order to create a community of accessible knowledge for peer-to-peer support.

3. Collecting evidence across sectors:

Given the identified need for additional evidence, data should be collected across cannabis prescribing in all settings for specific products, for specific indications, and with a clear distinction in terms of the delivery mechanism and dose. Furthermore, the analysis of patient experience data for specific products would support both informed prescribing and the collation of broader real-world evidence. Accounting for each prescription and gathering an in-depth body of evidence in a range of forms can then be reported back in a feedback loop to further consolidate the knowledge base.

4. Launch a clinician-centred campaign:

Due to the lack of general knowledge and awareness of cannabis in the medical community, a national campaign should be launched amongst clinicians and medical professionals to increase appropriate prescribing in normal clinical settings and signpost relevant information, training and support.

5. Consider cannabis as per other medicines:

A clear stigma within the medical community has emerged from this research in terms of cannabis as a product. Given the drug's illicit nature and its recreational associations, clinicians are hesitant to engage with or to prescribe due to its status as an unlicensed, special medicine. However, since there are numerous other unlicensed medicines that are not treated with the same degree of resistance, the focus must be placed on evidence rather than emotion in terms of biases against prescribing cannabis.

6. Conduct more RCTs to supplement the knowledge base:

The development, implementation and funding of RCTs is of particular importance to bringing new clinicians on board and stimulating interest in prescribing medical cannabis. Higher quality RCTs are required, and although some are already underway, there are other forms of evidence that can inform and facilitate prescribing. The current knowledge base needs to be accessible and signposted to clinicians at the point of care, so they can prescribe based on the best available evidence. Unless the cannabis industry is more successful in engaging clinicians on indication-specific product evidence, we are unlikely to see mainstream market access to CBPMs.

Chapter 1: Introduction

History and Background

Cannabis has been employed as a medicine dating back to ancient times.[1] However, its illegality in the United Kingdom (UK) dates back to the Dangerous Drugs Act 1920[2] and the Misuse of Drugs Act 1971,[3] with these policies rendering research into the medical applications of the drug extremely challenging. Nevertheless, hesitations in carrying out research into cannabis have not been based on science but rather historic stigma, which has led to cannabis being treated differently to other pharmaceutical products and medicines.[4] The stigma surrounding cannabis has conflated its therapeutic benefits with its harmful recreational effects, overshadowing reasoned arguments for expanding research and medical access.

On 1 November 2018, medical cannabis was legalised in the UK,[5] following two high-profile cases of epileptic children that benefited from the use of the drug. Medical cannabis was moved from Schedule 1 to Schedule 2, with the UK Government recognising its medical benefits.[6] This change in policy enabled licences to be issued by the Home Office[7] to import medical cannabis.

The campaigns and subsequent legalisation of medical cannabis allowed the British public to connect with the compelling stories of suffering within families, and significantly increased public support for the drug. These media campaigns pressing for a change in legislation led to public outcry due to the life-threatening situations of young children whose suffering could be eased through the medical properties of cannabis.[8] This successfully shifted the profile of medical cannabis that was reframed through emotive responses.

Undoubtedly, the 2018 scheduling change has reduced the cost and challenges of conducting scientific research into cannabis. However, barriers to access remain, leading to a lack of appropriate research being undertaken. For example, although the UK has officially acknowledged cannabis as having legitimate medical uses, there are still significant barriers to medicalising cannabis and limitations to how it is currently prescribed.

Overview of the Current Model

Current UK policy allows patients to be prescribed medical cannabis for a select number of conditions. Despite the change in legislation four years ago, there are currently less than 20,000 patients[9] in the UK receiving medical cannabis, while over 1.4 million[10] UK citizens self-medicate via the illicit market. Therefore, there is broad acceptance amongst experts that this imbalance needs to be addressed due to the clear harms that arise due to prohibition.

A number of private clinics across the UK allow for patients to obtain a private prescription for medical cannabis with a qualifying condition.[11] Although any specialist clinician can prescribe CBPMs, there is a lack of willingness amongst clinicians to do so, due to the paucity of evidence. Thus, in the UK cannabis is largely prescribed through cannabis-specific clinics. NHS guidance[12] states that medical cannabis should only be prescribed when other treatment options have been exhausted and when there is clear, published evidence. At the moment, only the Epidiolex and Sativex products are available on the NHS and licensed in the UK, which are only prescribed in rare cases.

The current prescribing model through cannabis clinics does provide a quick route of access for patients and prices are reducing, the costs are still prohibitive in many cases. Nevertheless, such an approach is not aligned to the UK healthcare sector as no other medicine has such dedicated clinics, rendering cannabis-specific clinics as an anomaly.

Since the majority of private prescribers also work in the NHS, it is likely that their stance on medical cannabis remains inherently conservative. All of these combined forces contribute to cannabis prescribing remaining on the fringes of clinical prescribing practice.

In order for this situation to improve, it is clear that the evidence gap for medical cannabis must be addressed. There is also a need for more buy-in and support from existing specialist clinicians. If the current model does not develop further, there will be insufficient data to expand on the pharmaceutical benefits of cannabis and long-term medicalisation. There is also a need to change the current prescribing model in order to enable improved patient access.

Report Focus

Although cannabis has medicinal benefits and the UK's regulatory structure permits its use, there has been limited growth as a result of too few clinicians prescribing.

This report will (i) examine the current barriers for medical cannabis and how best to overcome them; (ii) explore how cannabis can be prescribed for specific conditions and the benefits of such treatment; (iii) seek to understand how clinicians can be effectively engaged in the issue; and (iv) consider a number of key issues and themes, as detailed below:

Moving Towards Medicalisation

Post-rescheduling, there is a need to place medical cannabis in the existing medical framework to facilitate its legitimation process. Therefore, cannabis requires a more medicalised approach to prescribing through the use of structured data.

Currently, there is a disconnect between cannabis-prescribing clinicians and their non-cannabis-prescribing counterparts, creating rather a sharp divide that is uncharacteristic of other areas of medicine.

In order to tackle this, it is necessary to help specialist clinicians feel more confident in prescribing and to explore models besides the current cannabis-clinic option.

For medical cannabis to obtain the legitimacy it deserves in the medical world, efforts should be focused on its integration into pharmaceutical practice. Advocacy efforts for expanding patient access have largely focused on separating medical cannabis into its own category. However, this approach lacks structure and represents a major barrier to medicalisation. Although significant policy progress has been made in the last four years, the UK's model requires diversification to see growth in the body of evidence and patient numbers.

Impact of Recreational Markets on Medical Research

We will also discuss the impact that recreational cannabis markets can have on medical markets and explore the challenge that the dual use of the drug can present for its medicalisation. The substantial nuance around separating recreational and medical cannabis use will be considered, as well as opportunities for the long-term, sustained development of effective cannabis medicalisation. However, this report does not extend into any detail on the recreational market or argue in its favour, since the focus is strictly limited to the prescribing of medical cannabis.

A Data-Led Approach

To compile this report, we spoke directly to clinicians to ascertain how the legitimacy of medical cannabis can be increased, while considering how a structured, data-led approach could positively impact on patient access and clinical buy-in across the UK. The report seeks to ascertain what an appropriate prescribing model in the UK could look like, to help build comfort and confidence amongst clinicians in the context of cannabinoid medicine.

Hypotheses

This report hypotheses that concerns will largely fall into two key limiting factors impacting clinicians in their confidence to prescribe medical cannabis:

H1: The complex, largely misunderstood clinical governance procedures and the irregular prescription fulfilment process is a limiting factor for clinicians.

H2: The lack of known efficacy for specific products to treat specific indication areas and a lack of prescribing history is a limiting factor for clinicians.

Chapter 2: Summary of Emerging Evidence

The medical cannabis industry lacks high-quality, large-scale randomised controlled trials (RCTs), which limits the conclusions that can be drawn in terms of the safety and efficacy of medical cannabis. The lack of research is often attributed to the legal status of cannabis, the associated stigma, its psychoactive effects, the challenge of standardising the product and how dosing is delivered. Furthermore, the number of active ingredients within the plant make it difficult to attribute efficacy to specific cannabinoids.

That said, there is an emerging body of evidence regarding cannabis use for the treatment of a variety of conditions, partly through its interaction with the body's endocannabinoid system.[13]

The cannabis plant has been used medicinally for thousands of years, but only in the last two decades has there been an emergence of scientific evidence to examine the medical benefits of cannabinoids.[14]

This chapter provides an overview of the conditions that have emerging evidence for medical cannabis treatment, presenting the current state of evidence and outlining the potential benefits of medical cannabis as an option when other treatments have been shown to be ineffective.

A comprehensive literature review conducted in 2020[15] revealed that the most robust evidence suggests medical cannabis may be effective in the treatment of chemotherapy-induced nausea and vomiting, seizure disorders, and multiple sclerosis (MS)-related spasticity and pain, although the evidence remains largely inconclusive. Moreover, a need was identified for consistency in trial design to enable the comparison of study findings. The establishment of indication-based treatments could also help lead to higher quality clinical evidence.

Pain Disorders

There is a compelling body of emerging evidence around the effectiveness of cannabis in treating pain. Pain disorders are difficult to treat, while assessing the effectiveness of treatments is also challenging due to the subjective nature of the pain experience.[16] The vast majority of pain studies also employ self-reported outcomes to assess effectiveness, which have certain limitations. The complex nature of conditions involving chronic pain and the lack of a clear, quantifiable dichotomy for pain renders it inherently difficult to study.

Few RCTs have examined the efficacy of medical cannabis in chronic pain. However, a prospective large-scale cohort study assessed the long-term effects of medical cannabis on chronic pain outcomes, finding statistically significant improvements in pain intensity and a decrease in opioid use,[17] with these positive outcomes sustained at one year follow-up. Treatment responses also did not measurably differ between patients that had previously used cannabis, and those who had not.

Evidence from prospective studies demonstrates that medical cannabis is effective in pain management with long-term improvements. Since it is particularly challenging to treat chronic pain and the standard of care medicines are problematic due to their risk of abuse and opioid dependency, the supportive evidence of CBPMs may be more compelling for clinicians to prescribe.

Symptom Alleviation

Review studies have shown effectiveness for the treatment of pain using cannabis,[18,19] along with it being safe and effective for other symptoms associated with chronic pain such as insomnia and anxiety[20] compared to standard medications. A crossover trial[21] demonstrated that cannabis is well-tolerated in patients, improving symptoms and sleep.

Meanwhile, registry data[22] suggests that medical cannabis is effective in treating pain, with significant improvements in self-reported measures and few adverse effects.

Adverse Reactions

Cannabis dosing remains a challenge for administration, with no guidelines or established standards.[23] The biphasic properties of the drug make this even more difficult, as low doses can produce different effects, sometimes opposite to those resulting from high doses, which is an important consideration when adverse reactions to the drug are dose-dependent. However, cross-sectional research has demonstrated that cannabis has a better risk–benefit assessment than most other treatments.[24]

Opioid Reduction

Existing evidence demonstrates that cannabis can help reduce opioid consumption among chronic pain patients, mitigating the harm caused by opioid use. Self-reported questionnaire data supports the efficacy of medical cannabis for quality-of-life ratings in chronic pain patients over a six month period,[25] where the consumption of analgesic medication decreased with increased concentrations of tetrahydrocannabinol (THC) at a given intensity of pain.

The benefits of cannabis in pain management appear to be the greatest in patients with chronic conditions, particularly where opioids have proved ineffective.[26] Since cannabis is predominantly effective in treating chronic as opposed to acute pain, the reported quality-of-life ratings are of particular significance.

Conclusion–Pain:

There is an emerging body of evidence demonstrating the effectiveness of CBPMs for treating pain. The evidence is particularly compelling in terms of quality-of-life ratings amongst chronic pain patients and the reduction of harm caused by opioid medications. Despite pain being a challenging indication to treat due to its subjective nature and the need for self-reported patient outcomes in research, there is some evidence demonstrating that cannabis can represent an effective treatment for improving quality of life, symptom alleviation and harm reduction.

Mental Health Disorders

Research has investigated the potential for medical cannabis to treat mental health conditions. Nevertheless, such treatment remains controversial among clinicians due to the complex relationship between recreational cannabis use and mental illness, as a potential form of self-medication or due to comorbid substance misuse disorders. Regardless, this relationship has represented a barrier in terms of investigating the potential for treating mental health conditions, although there is emerging evidence from patients using cannabis to manage their symptoms of anxiety and depression, who report subjective improvement.

Medical cannabis treatment for mental ill-health is complex. The self-medication hypothesis argues those with anxiety disorders use cannabis to relax and better cope with stress.[27] What remains disputed is whether cannabis is effective in reducing symptoms, or whether it exacerbates them. It appears that cannabis has a biphasic or bidirectional effect on anxiety, meaning that patients experience relief from symptoms, but regular use could lead to the development of cannabis

use disorder coupled with worsening symptoms. The mental health indications for cannabis caution that the distinction between recreational and medical use can become particularly blurred, which is a key reason why research must examine indication-specific medications for this area.

A meta-analysis of 31 studies investigated the prevalence of anxiety disorders and cannabis use in the general population,[28] finding a positive association between anxiety, cannabis use and cannabis use disorder. However, a correlation between anxiety and cannabis use disorder does not necessarily imply causation. There is little direct evidence to support the contention that cannabis use causes anxiety, particularly as the natural history of some anxiety disorders is a slow onset and the severity of conditions at baseline is low. This could simply reflect how anxiety develops in the absence of cannabis, since causation cannot be meaningfully established through longitudinal analysis alone.

Post-traumatic stress disorder (PTSD) is an indication that is receiving increasing pharmacological and psychological interest in terms of medical cannabis treatment, through which retrospective research[29] found a 75% symptom reduction in PTSD patients. This is consistent with evidence[30] showing that the endocannabinoid system is involved in the regulation of emotional memory, facilitating the extinction of aversive experiences.

Much like other anxiety disorders, there is a strong link between trauma, PTSD and substance use disorder (SUD). The association between PTSD and SUD has been particularly well documented among military veterans, with SUD functioning as a coping mechanism for PTSD symptoms, such as the use of cannabis for its relaxing and calming effects. It is for this reason that many patients self-medicate with substances to mitigate distressing symptoms, with relief from anxiety representing a key rationale for using cannabis. Epidemiological studies, however, estimate that individuals with PTSD are 2–4 times more likely to suffer from SUD than non-PTSD subjects.[31, 32] Despite the complex interaction between self-medication, symptom relief and medical cannabis use, research does show promise in the treatment of mental health disorders.

Conclusion–Mental Health:

It is important that the link between PTSD and medical cannabis use is studied in greater detail, which will benefit the treatment of other mental health conditions. Although the evidence regarding the use of medical cannabis to treat mental health conditions is not conclusive, research shows that it can be effective in helping to manage PTSD, which warrants further investigation. Furthermore, given the level of concern surrounding existing pharmacological treatments for PTSD, medical cannabis should be viewed as a viable treatment for some patients with greater efficacy and improved symptom management. However, caution is necessary due to the complex relationship between recreational cannabis use and mental illness, particularly in the context of self-medication.

Gastroenterological Disorders

Cannabis is known for its antiemetic, appetite stimulating and antidiarrheal properties, which indicate that it may benefit those with gastroenterological disorders.[33] Therefore, cannabis has traditionally been used to treat intestinal inflammation, with an increasing cohort of patients with inflammatory bowel disease (IBD) reporting its use for self-medication.

There is a growing body of evidence for cannabis treatment in ulcerative colitis (UC), a type of IBD. A double-blind randomised placebo-controlled trial examined treatment outcomes for UC patients using cannabis, finding that short-term treatment with THC-rich cannabis was associated with clinical remission and improved quality of life.[34]

Crohn's disease is another form of IBD, which is difficult to treat and has no cure. Many clinicians of Crohn's patients thus turn to other treatments to support their wellbeing, including medical cannabis. A randomised double-blind placebo-controlled study investigating the effects of the oral use of cannabidiol (CBD) rich oil for Crohn's disease outcomes found that after eight weeks of treatment, there was reduced disease activity, improved quality of life and immediate symptomatic improvement, with the treatment well tolerated throughout.[35] Furthermore, a small-scale placebo-controlled study[36] concluded that a short course of THC-rich cannabis produced significant clinical benefits in patients with Crohn's disease, without evidence of additional side effects.

A Cochrane Review examined the safety and efficacy of cannabis treatment in the two available RCTs for the indication. Although for remission rates cannabis did not demonstrate a clear benefit compared to placebo, there was higher self-reported quality of life among patients prescribed cannabis,[37] with quality of life of particular importance for those affected by a chronic condition.

These encouraging results from the RCTs have been supported by additional published prospective research. A study of 292 IBD patients revealed that a significant number used cannabis to treat a range of symptoms.[38] Another prospective observational study assessed the effects of cannabis use among 127 IBD patients,[39] whereby the cannabis group had statistically significant weight gain (an important metric in diseases that can cause weight loss), while their intake of other medications significantly reduced. It is worth noting that in these studies, no relevant side effects were reported as a result of cannabis use. These studies thus further support the hypothesis for clinical improvements in IBD with medical cannabis treatment.

Conclusion – Gastroenterology:

There is an emerging body of evidence for medical cannabis to reduce the symptoms of gastroenterological disorders, an indication that has been difficult to treat conventionally. Although studies have been small, the RCT data show promising results, with a key takeaway being strong quality-of-life improvements.

Neurological and Movement Disorders

Medical cannabis has therapeutic potential for a broad range of neurological and movement disorders with few side effects, with research reporting a positive impact on a number of conditions through the product's neuroprotective, anti-inflammatory and immunomodulatory properties[40] that help to reduce relapse rates, as well as the intensity and impact of symptoms. There are, however, several adverse effects that need to be considered when prescribing, ranging from nausea to mood changes, although these reactions can be mitigated through careful prescribing.

A systematic review[41] examining the efficacy and safety of medical cannabis in several neurological disorders concluded that the concentration and ratio of THC to CBD plays a key role in the therapeutic effects, with medical cannabis showing effectiveness in reducing long-term patient-reported scores for spasticity, central pain and bladder dysfunction.

Nevertheless, clinical trials have not been sufficiently consistent to demonstrate beneficial effects unequivocally, and thus there is no definitive clarity regarding the effectiveness of cannabinoids in the treatment of movement disorders.

Multiple Sclerosis

There is a growing body of evidence highlighting efficacy in CBPMs treating MS symptoms, and in particular spasticity,[42] due to cannabinoids' well-established anti-inflammatory properties.[43] Whilst evidence indicates that cannabinoids provide symptomatic improvement in MS,[44] systematic reviews found the effect on spasticity and pain to be at best moderate.[45]

Medical cannabis is reportedly effective for a range of MS symptoms[46] including pain, stress, insomnia, mood swings and muscle spasm. Given its effectiveness in reducing more than merely pain and spasticity, cannabis occupies an important space in terms of increasing the quality of life in patients, which should be further considered by clinicians.

Epilepsy

CBD is associated with a sustained reduction in seizure frequency and severity for epilepsy, which has been supported by open-label studies, observational studies,[47] RCTs[48] and large-scale systematic reviews.[49] However, while CBD appears to be effective in treating epileptic seizures, the underlying mechanisms remain unclear.[50]

Overall, there is an evidence base for the safety and efficacy of CBD administration for treatment-resistant epilepsy,[51] although bioavailability issues and a lack of dosing standardisation have hindered the adoption of CBD-rich medical cannabis in mainstream seizure management.[52] Given the evidence for reducing seizures, the increased prescribing of medical cannabis should be considered.

Given that Epidiolex is licensed, clinical data holds value to substantiate the claims for its use. Thus, there needs to be greater awareness of the benefits available for clinicians to consider it as a treatment option.

With regard to the benefits for epilepsy patients, it is worth noting that the current licensing for medical cannabis is restricted for use in rare syndromes.

Gilles de la Tourette's Syndrome

Retrospective case report data suggest that cannabis is well tolerated in Tourette's patients. In particular, treatment-resistant patients reported benefits from using THC-rich cannabis with improvements in tics, comorbidities and quality of life in the long term.[53] While there may be insufficient evidence to support its widespread clinical use, with existing studies featuring an uncontrolled design and retrospective data analysis, it is important to recognise that medical cannabis can be a safe and effective treatment in at least a subgroup of adult Tourette's patients, for whom there are currently limited treatment choices.

Parkinson's Disease

Cannabinoids appear to demonstrate neuroprotective effects in Parkinson's disease, and although the results remain inconclusive,[54] there is a suggestion that CBD improves the quality of life in patients regardless of comorbid mental ill-health. These promising findings require further study in terms of the dose, formulation and target patients.

Conclusion – Neurological & Movement Disorders:

There is an emerging evidence base for cannabis treating neurological and movement disorders with few serious side effects. However, it is still necessary to clarify the pharmacological, physiological and therapeutic effects of medical cannabis for movement disorders, partly due to gaps in our understanding of the effect of cannabinoids on motor pathways.[55] Many methodological differences and discrepancies also remain in studies investigating medical cannabis, which makes it difficult to reliably conduct comparative analyses, thus underscoring the importance of implementing a structured data approach. Although there is a mixed level of efficacy for neurological and movement disorders, overall there are promising findings to indicate medical cannabis can offer quality of life improvements when other conventional treatments have not been successful.

Discussion

There is an emerging body of evidence to support medical cannabis as an effective treatment in a range of indication areas, alongside recognition that randomised, placebo-controlled trials may be necessary for market authorisation to ensure these medicines are available through the NHS. Nevertheless, the current evidence supports more widespread prescribing than currently is the case. Therefore, if this evidence is compelling and growing, why are UK clinicians still not prescribing medical cannabis?

One reason may be that the evidence has not been adequately presented to clinicians in a compelling manner.

Thus far, there has been a disconnect between the evidence base and its communication to clinicians, which this report aims to address. The UK demand for medical cannabis to date has been patient-led with virtually no regard to clinical evidence, relying on personal recommendation and anecdotal evidence. However, in order to move towards an evidence-led model, clinicians must be presented with robust data that can lead to increased levels of prescribing.

Although existing evidence holds promise and suggests that cannabis may be effective, there is little structure to how this is being approached, leading to the conclusion that a lack of evidence may not be the problem with cannabis prescribing, but rather that the evidence being produced is of insufficient quality. A large proportion of the research to date has remained highly conventional, examining cannabis as a generic medicine rather than the individual components of the plant, which is unlikely to provide sufficient knowledge and confidence for clinicians to prescribe. Therefore, in order to expand patient access, more product-specific data is necessary to allay clinicians' concerns.

The emerging evidence to date raises important discussion points regarding clinicians' recognition of the substantial number of patients, with a broad range of conditions, that currently could benefit from CBPMs to improve their overall quality of life.

Chapter 3: The State of the UK Cannabis Industry Today

The UK medical cannabis industry has received significant hype since its inception, and regardless of whether the focus is on the curative properties of the drug, or the market size estimates for this seemingly lucrative sector, medical cannabis has been positioned as an exciting, novel domain. However, despite its significant potential, the market has remained small, and is still largely positioned on the fringes of the healthcare system.

Advocacy Drives Policy Change

Despite cannabis clinics being an important facilitator for expanding access, they have directed patients and clinicians towards a separate clinical pathway, away from mainstream practice.

Advocacy efforts to liberalise medical cannabis have been almost entirely driven from the bottom up, through individual patient stories and dedicated campaigning on their behalf. This approach is essential at the onset of any advocacy work, in order to draw attention and create an emotive response. The campaigns in 2018 achieved precisely this, through realising a compassionate acknowledgement from the general public, media outlets and policy makers. However, while effective in raising the profile of the issue, progress has plateaued, whereby the advocacy efforts have proven reactive with the lack of a realistic strategic vision for medical cannabis access in the UK. Therefore, although patient demands for NHS access are justifiable, little progress is unfolding at this time.

This begs the question, why is NHS access unrealistic if medical cannabis is now legal?

The sudden policy shift witnessed in 2018 did not involve clinician engagement, and was in many respects a knee-jerk reaction to several high-profile public campaigns. This lack of clinical engagement has proven problematic, since clinicians are a key stakeholder group that must be consulted if the industry seeks widespread access.

Barriers to Prescribing

There are in excess of 40,000 specialist clinicians who are eligible to prescribe cannabis across the UK, yet only approximately 100 (0.25%) are actively doing so, which suggests there are more challenges facing clinicians than purely political concerns. Therefore, it is vital to understand the reluctance to prescribe cannabis, and what needs to change.

Ultimately, the medical cannabis industry has not been sufficiently focused on positively engaging clinicians, with a dominant industry narrative involving the cost of medical cannabis. Although this is a legitimate concern for NHS Trusts and patients at private cannabis clinics, the conversation should focus on the efficacy and safety of medicines, which would ordinarily play a more central role in a clinician's prescribing decision. This shift is necessary in order to increase awareness of the benefits of medical cannabis and lead to the eventual uptake of cannabis prescriptions. However, the focus on cost and NHS access has meant that developments in research and efficacy studies have been downgraded to secondary considerations, which has limited awareness of the cannabis plant's therapeutic benefits and therefore fundamentally restricted the number of interested prescribers, leading to low patient access.

If medical cannabis is to become mainstream, clinicians' confidence to prescribe must be addressed. Therefore, a clinician-centred model is required. Clinicians fundamentally have their patients' best interests at heart, but are naturally conservative when presented with a botanical treatment, particularly one with unconventional delivery mechanisms, a history of patients' self-medicating usage and with links to the illicit drugs market.

Another recurring theme is low patient numbers, which has led to medical cannabis's prohibitive cost, since the size of the industry has not grown in line with initial expectations. This issue is partly attributable to the poor uptake from clinicians. However, if more were willing to prescribe, patient numbers would increase, and costs would decrease.

There is also a clear lack of understanding and education regarding the complexities of the cannabis plant, as well as the intricacies of the current regulatory structure. For example, the widespread acceptance of CBD products found in many high-street retailers has led to a misunderstanding of what the medical product actually is, what it helps to treat, and its legal status.

The Role of the Cannabis Clinic

Cannabis clinics have shaped the landscape of the industry thus far, with the clinical model creating patient access points and representing a collective intermediary solution for the prescribing of medical cannabis. Such clinics have been an essential means of promoting the use of cannabis in the UK, acclimatising the healthcare system to its indications and potential.

There is a necessary distinction to make between private practice and the NHS. Understandably, NHS practice is based on proven clinical validity and cost-effectiveness, with a need for rigorous RCTs and a systematic cost–benefit approach when using taxpayers' money. Clinicians working in private clinics may be less conservative. In fact, part of the belief from the patient's perspective when seeking private healthcare is the expectation for receiving slightly more than the NHS provides, with the assumption that the clinicians will be more flexible and innovative in the treatments they offer.

Although cannabis clinics have played a role in stimulating the industry, the model has in some respects exhausted itself. While such clinics were intended as a first step towards initiating prescribing and broadening access, the momentum has been lost as patient numbers are not increasing as quickly as expected, with cannabis prescribing not becoming normalised within mainstream medicine.

The cannabis sector has remained isolated and distinct from the broader UK healthcare sector, which is problematic when attempting to integrate a new medicine and fundamentally limits scalability. Essentially, there is a lack of awareness and knowledge outside of the medical cannabis community, both amongst clinicians and patients.

Since specific clinics for specific medications are not common practice in healthcare, why should we adopt this approach for cannabis? Albeit unintentional, this approach has marginalised cannabis treatment still further and created a form of exceptionalism. A clinic dedicated to a single product inherently creates a prescribing bias, as opposed to encouraging an appropriate, balanced and ethical approach. In order to bring cannabis-sceptic clinicians on board, we need to transition away from this clinic model towards integration more broadly into existing clinical settings.

The essential task of engaging specialist clinicians in cannabis prescribing remains in its infancy. Despite over four years having passed since the policy change, there are few patients with cannabis prescriptions, and only a paucity of clinicians prescribing. Given the time that has elapsed, it is evident that the industry's approach needs to be adapted and expanded. To better understand why clinicians lack confidence and a willingness to prescribe cannabis within their own clinical settings, Chapter 5 of the report will investigate this issue through the first-hand perspectives of specialist clinicians in the UK. Before that, Chapter 4 will describe the methodology applied to collect and analyse the qualitative interview data for this report.

Chapter 4: Methodology

This report utilised a qualitative methodology to conduct an in-depth examination of the perceived barriers and solutions of UK-based clinicians regarding medical cannabis prescribing, with semi-structured interviews conducted to gather their insights. The use of the semi-structured interview enabled the researcher to deviate from the interview schedule and facilitate the introduction of new perspectives when relevant, as a result of the interviewees' responses. This instrument was thus selected to ensure that rich and detailed data could be gathered from each participant.

Specialist clinicians from the areas of neurology, gastroenterology, pain medicine, rheumatology and psychiatry were interviewed. These particular branches of medicine were chosen as they contain the indications for which CBPMs are prescribed in the UK today, as well as representing where the largest body of evidence currently lies, thus underscoring the relationship between existing research and prescription patterns.

Interviews with organisations in the medical cannabis industry were also conducted to gain a perspective on the existing solutions and innovative steps already taking place to address the issues which were identified during the research, in regards to medical cannabis prescribing.

A total of 52 interviews were conducted. 41 of which were conducted with clinicians and academics in the fields of psychiatry (n=15), neurology (n=10), pain management (n=7), gastroenterology (n=7), rheumatology (n=1) and a general practitioner specialising in substance misuse (n=1). 11 were conducted with organisations in the medical cannabis industry. All interviewees gave their informed consent to participate in the research.

The semi-structured interview data were analysed thematically using Braun and Clarke's (2006)[56] six-step framework (see Table 1), to lay the foundation for the analysis presented in Chapter 5. Therefore, the qualitative data gathered through these semi-structured interviews informed the conclusions of the report. All interviews were audio-recorded with the interviewees' consent, and then transcribed. These transcriptions formed the basis for the subsequent thematic analysis to be carried out.

Phase	Description
Step 1. Become familiar with the data	*Transcribing interviews, reading and re-reading data, noting down initial ideas.*
Step 2. Generate initial codes	*Coding interesting features of the data in a systematic fashion across a data-set, collating relevant data to each code.*
Step 3. Search for themes	*Collating codes into potential themes, gathering data into each potential theme.*
Step 4. Review themes	*Checking if themes work in relation to the coded extracts, generate a thematic map of the analysis.*
Step 5. Define themes	*Redefining specific of each theme.*
Step 6. Write-up	*Selecting vivid and compelling examples, final analysis of extracts and relating analysis back to hypotheses.*

Table 1. Braun and Clarke's (2006) Thematic Analysis Framework

Chapter 5: Listening to Clinicians

In light of the limited engagement to date with clinicians on the topic of medical cannabis, this chapter of the report is dedicated to providing a platform for their views to be heard. We interviewed a range of specialist clinicians to understand the origins of their hesitancy regarding cannabis prescribing. These interviews focused on ascertaining the basis of their reservations towards cannabis and determining what would alleviate their concerns, with the clinicians providing a range of opinions regarding their disposition and degree of confidence in prescribing cannabis.

It is important to note that a limiting factor within this analysis is the nature of the self-selected sample that may bias the results, since only those individuals who felt they knew sufficient depth about the subject and were comfortable to discuss medical cannabis responded.

Through the thematic analysis, three key themes emerged from the data regarding what specifically contributed to a clinician's hesitation to prescribe cannabis:

1. Evidence
2. Governance
3. The perceived uniqueness of cannabis

Within each theme a variety of subthemes were identified, detailing a range of discussion points. Both evidence and governance were identified early on in our hypotheses as key barriers perceived by the clinicians, with the final theme of the perceived uniqueness of cannabis identified as an additional limiting factor.

Theme 1: Evidence

The perceived insufficiency of the evidence base for medical cannabis was identified by the majority of the clinicians as the most significant barrier to their willingness to prescribe, with the available evidence on both the safety and efficacy of medical cannabis considered to be insufficient.

> *"I would have no hesitation about prescribing it, if and when it is proven to work and it is regulated. If you start doing things that are not evidence-based and are not proven to be safe, it is bad practice. It's not just that it is individual hesitancy, you're actively told not to do that as a doctor. It's the first 'do no harm'. I think most doctors are a bit suspicious of people who give a lot of unproven treatment...what you've got to do has got to be rooted in science, that's what medicine fundamentally is. You've got to show something works, to prove it's effective."*
>
> **Dr Chris Derry**
> **Neurology**

The sentiment amongst most of the clinicians was largely that the evidence base for the widespread prescribing of cannabis is simply not yet available, and that they would want to see higher grade evidence before prescribing.

Lack of Efficacy

Some clinicians explained how the data available for their specialty showed that medical cannabis has benefits that are unremarkable or modest at best. Especially when considered alongside the extremely high costs of CBPMs, they did not feel that the benefit to patients would justify them prescribing a CBPM over a more cost-effective medication.

This was especially noticeable amongst the neurologists in terms of treating epilepsy, who did not feel that current trials show that cannabis is particularly special or preferable over other anti-seizure medications.

> *"For the patients, what helps make a difference is if they are seizure-free. You see a 50% seizure reduction—and I agree with it as a regulatory outcome—but for the patient, if they jumped from the 5th floor, instead of the 10th, 50% reduction? It's going to have the same impact."*
>
> **Prof. Ley Sander**
> **Neurology**

Furthermore, some felt there was a significant discrepancy between the breadth of claims made by patients and advocates regarding the efficacy of CBPMs, compared to the proven benefits. In many cases, this added to the clinicians' scepticism as they felt that the support for CBPMs was based largely on ideology, as opposed to evidence.

> *"…show me a trial that it works, show me a series of trials it works and how we should use it, where we should use it and if it's got efficacy; you show me that and I'll use it. The notion that I'm sitting here and saying, "I don't believe these drugs work therefore I refuse to even countenance them", that's just not the way we work in medicine, and particularly not in epilepsy."*
>
> **Prof. John Leach**
> **Neurology**

Type of Evidence

There were multiple dimensions to the concerns regarding the perceived lack of evidence, with available evidence generally perceived as being of the wrong type and of insufficient quality. Most of the clinicians reported that in order to confidently prescribe they would need to see RCT data on medical grade products, demonstrating the efficacy and safety of CBPMs.

> *"A good RCT is a good RCT. That's all I want to see."*
>
> **Dr Edward Chesney**
> **Psychiatry**

> *"The first thing that is needed from my perspective is standard, medical grade evidence, so RCTs of a pharmaceutical grade drug. Once you've got those, you have something to work from."*
>
> **Dr Chris Derry**
> **Neurology**

The clinicians also expressed how this lack of RCT data plays a significant role in the restrictive nature of the guidelines established by the medical governing bodies. Some felt frustrated by the ineffectiveness of the real-world evidence and patient anecdotes. This was in part due to the difficulty in standardising the type and dose of CBPMs across patients, and the inherent bias that anecdotal evidence presents.

> *"It is hard to get beyond the evidence—it needs to be of high quality. At the moment, we've ended up with a lot of low quality evidence.*
>
> *A couple of RCTs for an indication would be game-changing and would make a huge difference. We talk a lot about evidence for cannabis, but it is about the type of evidence too. I see no reason once getting into isolates that you can't run RCTs. Right now we're seeing the sector trying to build evidence with biased observational studies. The current model is giving cannabis to patients that want cannabis and want it to work."*
>
> **Dr Euan Lawson**
> **General Practitioner**

The clinicians emphasised how prescribing CBPMs in the absence of RCT data, considered the gold standard for new medications, would go against the central tenets of their role as clinicians.

"We have to understand that under the word 'evidence' there are different types of evidence. Although real-life evidence is invaluable, here we can't have real-life evidence, it is not standardised."

Dr Radu Tanasescu
Neurology

It was recognised that a significant issue with real-world evidence based on self-reporting by patients is the likelihood of reporting bias. A large proportion of those using CBPMs have approached their clinicians or cannabis clinics specifically to request cannabis for their condition, sometimes because they have already started self-medicating illegally. Due to their preconceived positive perception of cannabis for treating their condition, there is an expectancy effect, and therefore an increased likelihood that they will feel the expected benefits and report these to the clinician. Meanwhile, those clinicians prescribing at cannabis clinics are likely to have similarly positive perceptions of CBPMs, which further compounds this expectancy effect.

The clinicians interviewed for this report expressed concerns that this self-selection of treatment by patients creates a biased set of positive reports and is not necessarily reflective of how effective cannabis would be in cannabis-naïve patients, or the general population. This issue was especially noted in the context of pain, where the benefits are subjective and self-reported.

Nevertheless, within each specialty, there were varying opinions on the quality of the evidence base. Whilst most of the clinicians agreed that more RCT data was required, a number of clinicians felt convinced by the available evidence and believed that regulatory bodies and other clinicians were being overly cautious and restrictive. Some clinicians even expressed how they would take notice of other types of evidence, such as observational studies and positive anecdotal reports from multiple patients.

"One of the things I talk about in my philosophical articles is that randomised controlled trials are probably not the best way to look at some pain medicine because pain is not a single disease."

Dr Rajesh Munglani
Pain

"Very few randomised studies actually show impacts and, largely, it's because you look at visual analogue scores for pain—the experience of pain is a multidimensional experience and then we try to represent that on a zero-to-ten scale. So I think the way that we do the research causes failure."

Dr Terence Muldoon
Pain

CONDITION SPOTLIGHT

Neurology

The neurologists appeared to be particularly conservative in terms of cannabis prescribing, despite epilepsy and MS being licensed indications for prescribing. Many of the interviewed neurologists believed that CBPMs were, at best, only moderately effective, with a common view expressed that the reduction in seizures was not sufficiently significant to outweigh the barriers to prescribing.

"I think it's an average anti-seizure medicine. I think it's an anti-seizure medicine that is being pushed directly to the family groups and they're being mis-sold the notion that this is a treatment that would just cut down the seizures, which it has modest effect of against in some genetic epilepsies and congenital epilepsies….I don't think there is evidence to support it..."

Prof. John Leach
Neurology

The neurologists were also concerned regarding the long-term effects of cannabis prescribing and the lack of associated knowledge.

> *"Another problem is that with antiepileptic drugs…some of the chronic problems take a long time to come out. So you might have to give drugs on a regular basis for three years to see something like..."*
>
> **Prof. Ley Sander**
> **Neurology**

There was a clear discrepancy between specialties on the necessary level of clinical evidence. The gastroenterologists, for example, commonly believed that there was little evidence for the indications they treated, and the psychiatrists expressed the view that there was no evidence for the efficacy of CBPMs in treating psychological conditions, while the pain specialists acknowledged the potential efficacy of cannabis.

> *"No, not for me because in chronic pain there's a lack of evidence for most of the stuff we do. So that is not necessarily a game-changer."*
>
> **Dr W Allister Dow**
> **Pain**

CONDITION SPOTLIGHT

Pain Management

There were several positive points made surrounding the potential for pain patients uniquely to benefit from cannabis, with the pain clinicians highlighting that their patients often reported quality-of-life improvements from self-medicating. Thus, the clinicians were excited about the potential of medical cannabis, given that many of their patients faced few available treatment options.

Across the board, the clinicians were keen to avoid the use and prescription of opioids, with recognition among some clinicians that CBPMs could represent a promising alternative to reduce the harms caused by opioid addiction. Nevertheless, some pain specialists were hesitant to prescribe cannabis precisely due to the problems associated with opioid medication, and the risk of contributing to another similar crisis.

Due to the biopsychosocial nature of chronic pain conditions, some pain specialists were more comfortable prescribing without the need for pharmaceutical grade evidence of the effects on the patients' physiology, being largely comfortable with benefits that are often self-reported and linked chiefly to the psychological impacts of cannabis. These benefits include reduced anxiety, improved sleep and lower levels of depression that, in turn, improve patients' quality of life and their ability to manage their condition. Thus, many pain clinicians saw the value of prescribing medical cannabis to manage chronic pain or comorbid symptoms.

> *"...when you've tried all these other drugs like morphine, gabapentin, and they're not getting better—particularly if patients have high anxiety—my experience is that those patients may benefit from judicious doses of medical cannabis. And I've seen that happen; they have an improvement in quality of life. Interestingly, when you talk to them about the pain they say, "Oh yeah, the pain is there but it's not as bad", or "It doesn't worry me as much". So you can see that there are a number of different effects. Although the animal studies suggest that you get a very profound effect on some of the pain pathways, in human beings the anti-anxiety effect is actually quite important."*
>
> **Dr Rajesh Munglani**
> **Pain**

Consequently, some pain specialists expressed their uncertainty as to whether evidence for the efficacy of medical

cannabis in treating pain will ever meet the standard required by the regulatory bodies to loosen restrictions on prescribing.

Other pain clinicians were more reserved in terms of the notion of prescribing cannabis because of the associated psychological impact. However, there were concerns regarding frequent cannabis use leading to an elevated risk of mental health issues in general, particularly since psychological issues are often comorbid to chronic pain disorders.

With clinicians across different specialties holding disparate knowledge in terms of the quantity, quality and acceptability of the evidence available for their specialty, this indicates a need to clarify what level of evidence is required throughout the medical community in order to prescribe CBPMs.

Lack of Safety Evidence

Many clinicians highlighted concerns regarding the risks, side effects and long-term impacts of prescribing CBPMs to their patients, which would not be allayed until more evidence was available regarding their safety.

> *"I mean the other advantage of things that come with regulatory trials is we know things like: What is its safety in overdose? What do I advise to my patients that get pregnant? And with unlicensed products it is an absolute disaster. The kind of questions that people ask you, you just don't have the answers to. I appreciate that people feel that they are able to take that responsibility themselves; they are until the problems occur, and then those responsibilities are shared."*
>
> **Dr Rhys Thomas**
> **Neurology**

> *"I would like to see a complete data-set on the potential interaction, the teratogenicity, and the long-term safety. Of course, if I see problems with the safety, it's one thing, if I see problems with the efficacy it's something else, and if I see problems with the interaction it is something else, because they will have different ways of dealing with it. However, if I see that there is nothing on the safety, I haven't a clue about the efficacy long term, and I don't know about interactions. That's what I'm going to tell people."*
>
> **Prof. Ley Sander**
> **Neurology**

Some clinicians noted that their only exposure to the impacts of cannabis was in patients who had been self-medicating and had consequently suffered complications, thus eroding the clinicians' confidence in the safety of CBPMs.

> *"Some patients will advocate cannabis for nausea and for digestive diseases and some patients say that this is helpful to them, but the patients I see with digestive problems are far more likely to have side effects from cannabis than they actually get any benefit from it."*
>
> **Dr George Bird**
> **Gastroenterology**

Indeed, many clinicians were not willing to take the risk of their patient encountering serious side effects, both due to the potential damage to the patient's wellbeing, as well as the legal and moral ramifications on their behalf as the responsible prescriber.

In response to whether a lack of evidence surrounding safety for cannabis is a limiting factor in prescribing, some clinicians did not distinguish between cannabis and other prescribed medicines.

Psychological Risks

There were specific and significant concerns regarding the psychological effects of cannabis,

and particularly the link between cannabis and psychosis. Since the psychological issues are, arguably, the most well-known risk of cannabis use, even clinicians with little knowledge about CBPMs expressed this concern.

Many of the patients seen by the interviewed clinicians are considered high risk in terms of the psychological side effects of cannabis use, and with a large proportion of their patients already suffering from psychological conditions, the clinicians held real concerns that prescribing cannabis could exacerbate these. Whilst this issue was most prominent for the psychiatrists dealing directly with mental health disorders, clinicians from other specialties also emphasised the prevalence of psychiatric co-morbidities and poor mental health in their patients, often due to the distress caused by living with a chronic illness. Similarly, the clinicians were also concerned about their patients' heightened susceptibility to dependency. Indeed, it was highlighted that many of those patients considered to be at high risk of psychological side effects, such as depression and elevated levels of anxiety, are also those that would most likely benefit from using CBPMs, especially considering its analgesic effects.

> *"The group that benefits may also be the group to run into problems. It's less likely with medical cannabis because you know exactly what you're giving, unlike 'street skunk'. Part of the issue is how to approach it safely because one of the things about medicine is you always look at the risk-benefit ratio, so if you look at the standard studies, which show that you would be doing more harm than good if you just prescribed cannabis to the general population. It's how to select those patients out, and there has to be a learning aspect of that, and a cautious aspect to that, and a consenting issue about that. So we have to be really quite careful."*
>
> **Dr Rajesh Munglani**
> **Pain**

Nevertheless, many clinicians expressed that safety was not a significant concern as cannabis is generally understood to be a relatively safe drug when prescribed under medical guidance. The relative safety of cannabis compared to other medications appealed to some clinicians, especially when their group of patients have so few available treatments. Furthermore, the point was raised that many of the medications that are commonly prescribed are abused, and therefore as the risk of abuse should not take priority over the potential benefits of other drugs, this same approach should also be applied to cannabis.

> *"I think we need to be pragmatic, though, and understand that a lot of the medications that we currently prescribe are abused. Obviously, benzodiazepines, but even other things like gabapentin and pregabalin; in the last five years, pregabalin has become a huge drug of abuse, and that's something that's very widely prescribed within psychiatry, anti-anxiety medication, as well as other things."*
>
> **Dr Richard Braithwaite**
> **Psychiatry**

Several of the clinicians also emphasised the suffering endured by many of their patients, and the paucity of treatment options at their disposal, with their risk–benefit analysis leading them to be less concerned about the safety risks of cannabis when compared against the distress their patients are experiencing due to the absence of an effective treatment.

CONDITION SPOTLIGHT

Mental Health

Given the relationship between cannabis use and mental health issues, unique points were raised by the psychiatrists regarding their perspectives on prescribing medical cannabis.

The psychiatrists generally expressed greater support for and familiarity with CBD compared to THC-rich medical cannabis, due to the evidence and potential harms caused by the psychoactive effects of THC among those with serious mental health issues. Their positive approach to CBD also appeared to stem from its non-psychoactive normalisation in mainstream medicine as a safe and effective product.

"There's emerging evidence for CBD in anxiety and psychosis. A side project I've done has been surveying patients of psychosis and asking them if they would consider CBD as a treatment for psychosis. Over 80% were open to it… they're on an antipsychotic and they don't like it and perhaps this [CBD] is better."

Dr Edward Chesney
Psychiatry

"A lot of my patients are self-medicating, not only using cannabis, but purchasing CBD products…I think there probably has been a shift in psychiatric dogma over the last few years away from necessarily telling patients that cannabis is always bad to saying that, well, maybe if you're just using CBD, and not using THC, then maybe the CBD is not the worst thing. It might be of benefit to you."

Dr Richard Anderson
Psychiatry

"Coming back to it, I feel much more comfortable around CBD because I think it's just out there, it's been out there for a lot longer and seems to have a lot more literature around it."

Dr Premkumar Jeyapaul
Psychiatry

Some psychiatrists also voiced concerns about whether medical cannabis patients are likely to be clinically compliant, considering the accessibility of the illicit market.

"It's true, from a doctor's point of view, it would be ideal, but from a user's point of view, it's not necessarily a good thing to surrender the control of your substance use to a prescriber, because of the inhibition and the level of control."

Dr Justin Basquille
Psychiatry

Several psychiatrists mentioned cannabis being safer and potentially more effective when applied in combination with psychotherapy.

"I think, within psychiatric grounds, I think concurrent prescribing with therapy might be an added benefit, so if there's a wider context due to stressors or whatever, it makes sense to prescribe for a short period of time coupled with therapy."

Dr Premkumar Jeyapaul
Psychiatry

Drug Interactions

Another concern expressed by the clinicians centred on the insufficient available evidence on how cannabis interacts with other medications, a key factor to taken into account before prescribing medication. This was raised across all specialities, as many patients are already taking prescription medications, with many involved in multiple treatment regimes.

"People with epilepsy have a lot of comorbidities, so they might be taking a number of other drugs, a number of things, and I have no idea where to start. And I know that, because CBD is metabolised in the liver, it has a potential for a lot of interactions that are very individual. So if this was completely excreted, non-metabolised or it was excreted by the kidney, I would be more relaxed about it, but I know it goes to the liver. So, I know that this is asking for trouble."

Professor Ley Sander
Neurology

> *"...there is an interaction with other anti-seizure medicines and so the side effects around those interactions— with Clobazam and sodium valproate—are there. They are workable, and you can manage that by monitoring the liver function tests and making sure that you reduce the associated anti-seizure medicines, but the cost is a huge factor here."*
>
> **Prof. John Leach**
> **Neurology**

The uncertainties surrounding drug interactions were especially acute due to the complexity of the cannabis plant, which contains so many different compounds that clinicians felt they would need to know more about the specific side effects and interactions of the different compounds, namely, an evidence base that has not yet been fully established.

More research is clearly needed to understand the long-term safety of CBPMs, with clinicians currently feeling as though they are confronted with an essentially unknown set of risks and side effects. Nonetheless, the risks that have already been established, especially those concerning psychiatric issues and dependency, also play a role in the unwillingness of clinicians to prescribe CBPMs to their patients.

Indication Specificity and Compound Complexity

Another barrier outlined by the clinicians lies in the complexity of the cannabis plant, which contains a multitude of different cannabinoids, each of which has a different profile of potential benefits and side effects. Not enough is known about the effects of each cannabinoid, either in isolation or in different combinations, nor how these cannabinoids each impact different disease indications. This is a thus a barrier both to clinicians and to regulatory bodies, who are less likely to prescribe or approve CBPMs if the actions and effects of specific compounds are not yet known.

Some clinicians discussed the frequent assertions of cannabis proponents of its potential to be prescribed for a broad range of indications. This narrative that cannabis is a panacea has induced high levels of scepticism within the medical community. Confidence would be increased if specific compounds within the cannabis plant were identified, extracted and prescribed for specific indications, which would also bring cannabis more in line with the mainstream medical model.

> *"Having specific indications is essential, it can't just be about pleasure seeking— without a specific indication it just gets too close to a recreational product."*
>
> **Dr Euan Lawson**
> **General Practitioner**

> *"All I can say is that it would be so, so much easier if we know that the chemical is the thing that has the antidote effect, or those three chemicals in combination have an effect, and those are the things that are in this pill. That would just make the whole landscape so much easier to navigate."*
>
> **Dr Richard Braithwaite**
> **Psychiatry**

Whilst developing more indication-specific formulations using isolated compounds would increase the confidence of regulatory bodies and clinicians, this may not always be aligned to specific patients' needs. This was especially the case when the benefits of cannabis were felt through its impacts on the general quality of life, such as among chronic pain patients, rather than through having measurable effects on the indication itself.

> *"...the trouble with cannabis is that it has been sold as something for virtually everybody and, again, we like to know slightly more for specific indications and which group of patients might benefit."*
>
> **Anonymous**
> **Gastroenterology**

"It's certainly not going to get off the ground in the medical profession unless you have a specific definition as to where it's indicated and what it's licensed for. You can't just prescribe something because it might make a few people feel a bit better."

Dr George Bird
Gastroenterology

CONDITION SPOTLIGHT

Gastroenterology

Clinicians specialising in gastroenterology highlighted that their patients are often psychologically fragile as a result of their chronic condition, thus creating more concern around any potential psychological complications. However, similar to pain conditions, it might be the case that those most vulnerable to psychological complications may also be those who could most benefit from CBPMs.

The gastroenterologists stressed the limited existing treatment options for their patients who are often suffering comorbid conditions with myriad symptoms, and thus CBPMs could offer an important opportunity to minimise suffering. Surprisingly, the gastroenterologists appeared to be the least confident in the evidence base surrounding CBPMs for their specialty, despite the presence of RCT evidence in gastroenterology, and therefore there is value in reflecting on why this discrepancy manifests.

"In my field, I am not aware of any evidence, and certainly it has not percolated down to those that write guidelines for the rest of us, and that will be one major barrier, that there is not a foundation to base prescription on at the moment."

Anonymous
Gastroenterology

"I think it's been advocated as a useful painkiller but I've not come across any good trial evidence to show that it is superior to anything else."

Dr George Bird
Gastroenterology

Conclusion

The insufficiency of the evidence base for medical cannabis was a pertinent concern amongst clinicians. Both efficacy and safety were voiced as issues in terms of the confidence to prescribe, although this did vary by specialism: the neurologists appeared to be particularly conservative regarding prescribing CBPMs, while the gastroenterologists and psychologists also felt there was limited evidence. However, the pain specialists appeared to be the most open to prescribing, acknowledging the efficacy and potential for improvements in quality of life. Clinicians in all indication areas were concerned about the psychological risks due to mental health comorbidities amongst their patients.

Given the complexities of cannabis as a plant, many clinicians lacked a deep familiarity with it as a medicine, and felt that it did not dovetail into the medical model. The clinicians largely voiced their desire to see more efficacious RCTs due to their hesitancy to accept real-world data.

Theme 2: Governance

Concerns regarding governance and a general lack of understanding for the current prescribing process were a significant barrier for clinicians. Due to CBPMs currently being classified as an unlicensed special medicine in the UK, prescribing is restricted to clinicians on the specialist register of the General Medical Council (GMC).

Therefore, in order to prescribe a CPBM, they must receive permission from a controlled drugs accountable officer.

The GMC directly states that specialist clinicians "may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient".

Despite the GMC guidance requiring a multidisciplinary team to review the appropriateness for prescribing unlicensed medicine, governance procedures are lacking in terms of how this should be implemented. Therefore, clinicians bear all the risk when prescribing independently.

The vast majority of clinicians asserted that they lacked support in the form of guidance and information regarding the practicalities of the prescribing process. Many were unclear on how to access legal medical cannabis and the steps they would need to take to prescribe it to a patient. Knowledge was also absent surrounding dosage, administration and the length of treatment.

> *"Doctors just aren't sure how it works and have little understanding of infrastructure and governance. Not knowing the practicalities is a massive barrier as we need to be certain around how it is prescribed and administered."*
>
> **Dr Euan Lawson**
> **General Practitioner**

Peer Support

While the clinicians agreed with the GMC guidance regarding the requirement for the review from a multidisciplinary team, they acknowledged there was no infrastructure or guidance on such implementation. Improved support in this area would therefore boost confidence in prescribing.

A multidisciplinary team would facilitate discussion of each case, the input of a broader range of opinions and offer improved monitoring potential for any long-term side effects. Considering both the risk of adverse psychological reactions and the prevalence of mental health issues in the patients seen by the clinicians we interviewed, some highlighted the importance of having a mental health professional involved in the process, who could ensure ongoing psychological assessment.

> *"...it's going to be a complex interaction of both clinicians involved plus psychological assessment going through it, expectation and also being very frank about the side effects."*
>
> **Dr Rajesh Munglani**
> **Pain**

Moreover, the need for support stems from the risk clinicians currently face if they seek to prescribe unlicensed medical cannabis without the backing of a multidisciplinary team. Many clinicians felt that to operate outside of the current guidance would leave them vulnerable to criticism, political exposure and, were negative patient outcomes to manifest, medicolegal liability.

> *"…people are allergic to experimentation…. if you haven't got the support of your medical director and if you haven't got the support of the drugs and therapeutics committee, or if you've got their hostility or scepticism, you will not put yourself in the way of criticism. There's the odd maverick doctor who will, but it's a difficult position to be in—you're exposed."*
>
> **Dr Justin Basquille**
> **Psychiatry**

The clinicians explicitly expressed their fear of being reported to the GMC, and were conscious of risks to their medical licence.

Many emphasised the importance of reputation in their profession, and that the potential to damage their professional standing is significantly amplified when prescribing independently with no supporting governance infrastructure in place. In contrast, if prescribers are working in a team, then this introduces a support system that functions as a safety net of shared responsibility.

> *"The barriers have to do not so much with the lack of evidence, I think, as more medical social reasons…people are worried about standing out and being blamed if something goes wrong.*
>
> *You expose yourself, especially in the atmosphere that has prevailed over the last few decades in medicine, generally. There's a lot more regulation, and people have to answer more for what they do, and people feel less free to prescribe what they want...If anything goes wrong, it's all on your head… every doctor who is conscious lives with the fear of GMC referral and so your whole practice is governed by the avoidance of that."*
>
> **Dr Justin Basquille**
> **Psychiatry**

Education

Many clinicians expressed a general lack of knowledge and training surrounding medical cannabis, such as how it impacts the endocannabinoid system, what formulations are available, the indications it can be prescribed for, and the various benefits and side effects. This absence of structured education was also exemplified by the broad range of perspectives on the existence and validity of the evidence base, even among clinicians within the same specialty.

> *"Those are the sort of things I would want to know—Is cannabis oil A the same as cannabis oil B, and is that one any different to that one in its content. Because I don't even know how they make cannabis oil, I don't even know what it has got in it and so it's just an oil to me....I don't know anything about it at all."*
>
> **Prof. Peter Whorwell**
> **Gastroenterology**

> *"One thing is that, from a medical educational perspective, we are not very well aware that our body has receptors in the endocannabinoid system. We are alive with that neurotransmitter system in us so the endocannabinoid system is part of the normal homeostasis of a human species.*
>
> *And yes, there is a reluctance to prescribe. I can see it amongst my colleagues. They would prescribe it but would need to build experience with any medication. You can't start prescribing something on a daily basis unless you build yourself a bit of expertise. You have to have your own exposure as a medical practitioner."*
>
> **Dr Radu Tanasescu**
> **Neurology**

To remedy this, one suggestion was to create some form of feedback mechanism so that clinicians can learn from those already prescribing, especially as the knowledge surrounding prescribing is established through direct experience.

Although the clinicians appeared to want to learn from prescribers, cannabis clinicians in many ways practice within a closed loop and appear inaccessible, thus suggesting a need to open up and draw cannabis prescribing into the mainstream.

"If there was a way of gathering together people who are prescribing differently to learn from it, whether it's different products, different conditions, different outcomes, that would be very helpful in showing that information."

Dr Rhys Thomas
Neurology

Current NICE Guidance

A key barrier that arose was the perception of contravening current guidance, with the National Institute for Health and Care Excellence (NICE) guidelines cited frequently across the interviews, and the lack of detailed understanding regarding such guidance.

"The problem is, the recommendations from the big societies and from NICE, who just won't— it's a bit of a catch 22. The government won't recommend because the professional bodies won't recommend, and the professional bodies won't recommend because the government won't recommend."

Dr W Allister Dow
Pain

"People in the cannabis field have in mind that the regulators say it is okay, but what the regulator said doesn't have a translation in clinical settings."

Prof. Ley Sander
Neurology

Many of the clinicians were concerned about the burden on their practice, since whilst able to step outside of the guidelines if they feel the need, this involves the navigation of a number of regulatory and bureaucratic hurdles. Therefore, with their existing volume of caseloads, and considering the additional bureaucracy involved, taking on the task of prescribing cannabis would impose a significant strain on the clinicians' available time.

"In our minds, it is bound up with such a degree of regulation that it hasn't been worthwhile even exploring that."

Dr Justin Basquille
Psychiatry

"I've got to fill in the form to go to NHS England, I've got to hand write every prescription myself, I've got to organise all the safety bloods and tests, I can totally understand why other colleagues have chosen not to do that."

Dr Rhys Thomas
Neurology

"Within neurology, the main restriction would be the bureaucracy…..If I have a choice of two drugs and one of them has a dozen forms to fill in and one of them doesn't, I could imagine which one I'd prefer to use."

Dr Brendan McLean
Neurology

An additional obstacle involves the list of approved indications for the CBPMs licensed on the NHS, which are particularly limited at present.

"The reason cannabis is not being prescribed, it's because the licence indications are so narrow at the moment."

Dr Richard Davenport
Neurology

The clinicians also noted inconsistencies in the degree of restriction surrounding CBPMs. A clinician wanting to prescribe a CBPM (or any controlled substance) requires permission from a controlled drugs accountable officer in order to obtain a pink FP10 Controlled Drug prescription

pad, and the approval of their request is perceived to vary depending on the officer involved, thus leaving some clinicians to conclude that a somewhat arbitrary application of restrictions takes place.

> *"All of the controlled drugs accountable officers in the country should all have a template to work from so they are all doing the same thing. I heard the CD accountable officers for the other two paediatricians said yes, and mine is kicking up a fuss and saying she's not happy. That's not right."*
>
> **Dr Pramod Mainie**
> **Neurology**

Conclusion

Overall, the clinicians voiced a lack of support, along with insufficient understanding of the current infrastructure for prescribing cannabis. In order to increase their confidence in prescribing, clinicians require a clear framework on how to implement the guidance. Given the risk of prescribing outside of a team, the clinicians have concerns over their exposure to reputational damage without a supportive infrastructure in place. Moreover, the excessive bureaucracy in prescribing CBPMs is also a limiting characteristic for clinicians. Thus, ensuring clinicians are provided with the appropriate support within a governance framework and a prescribing process that is more streamlined is imperative to broaden prescribing practices.

Theme 3: Perceived Uniqueness of Cannabis

The vast majority of clinicians asserted an openness to learning more about prescribing medical cannabis, with many expressing active enthusiasm.

Considerable enthusiasm arose regarding the potential of medical cannabis to fulfil a pressing need for novel medicines, with many of the clinicians' patients suffering extensively through conditions that lack effective treatments at present. This issue was emphasised by the pain clinicians, who recognised the significant quality-of-life improvements experienced by their patients using medical cannabis.

There was also discussion surrounding medical cannabis as a promising alternative to prescribing opioids, rendering it as a potential harm reduction strategy. However, the illicit status of cannabis and its complicated socio-historical context render it subject to stigma.

Stigma

It was generally acknowledged that in terms of cannabis prescribing UK clinicians are broadly conservative. This is due to a number of factors including a duty of care towards their patients, the nature of the medical model they train under and work within (i.e. the NHS), and threats to their licence and reputation, as well as the many other barriers outlined in this report. This conservative attitude towards cannabis is exacerbated by the lack of knowledge among clinicians.

> *"The stereotypical view of cannabis is difficult to see past the smoking habit of it. Although it is emerging in other forms, they don't know much about it."*
>
> **Dr Euan Lawson**
> **General Practitioner**

However, some clinicians specifically mentioned their or their colleagues' stigmatised perceptions of cannabis, which included its potential as a gateway drug to broader substance abuse.

"You don't want to be in the vanguard, you don't want to be an isolated maverick practitioner prescribing and getting a name as being some sort of…because it certainly isn't quite respectable, because cannabis is viewed with that tainted aura of illegality."

Dr Justin Basquille
Psychiatry

"We need a broader raft of strategies to ease stigma and separate how people think about cannabis and opioids. It could be done through more research, evidence and a wider set of publicity. There is social stigma around weed and what it is—we cannot dissociate ourselves from the 1980s view of weed compared to the more nuanced understanding of cannabis now with the endocannabinoid system—this is something doctors cannot get their head around."

Dr Deepak Ravindran
Pain

Nevertheless, many of the clinicians explained that stigma was not a significant barrier to working in their patients' best interests, with some frustrated with the public perception that stigma and outdated views regarding cannabis were preventing them from prescribing.

"This idea that we are all puritans refusing to prescribe it in case patients actually feel good is utter nonsense."

Prof. John Leach
Neurology

"I think some of the major problems are the perceptions, so there's the perception on the public side that this is doctors just being awkward and wanting to deny patients successful treatments. Which is nuts. Funnily enough doctors are interested in finding successful treatments for their patients, but we do see some of the downsides and we recognise that there's no such thing as a wonder drug."

Dr Rhys Thomas
Neurology

Illegal Use

Some clinicians were concerned that, were they to commence prescribing cannabis, they would receive prescription requests from those wanting cannabis for recreational purposes, as opposed to a legitimate medical concern, and thus acquire a potentially problematic reputation as a doctor supportive of prescribing cannabis.

"I think it is incredibly important to distinguish therapeutic from recreational use. I think an awful lot of therapeutic use is the folks who want to get high getting their foot in the door, it is a problem….I do not want to have a reputation that 'this doctor prescribes medical cannabis' because then you get all sorts of crazy people…who come along with a bogus diagnosis wanting some cannabis prescribed."

Anonymous
Neurology

Another concern involved CBPMs being diverted to the illicit market, a situation that the clinicians had witnessed with opiates, for example.

> *"We have enough problems with diversion with opiates and then, even if you then reduce the supply, once people have tasted it and they have an addictive personality, they will continue to try and access this, and this is why you have a fentanyl epidemic in the States with illicit fentanyl coming in from China. And so people are worried that that will happen with medical cannabis."*
>
> **Dr Rajesh Munglani**
> **Pain**

Some clinicians recognised that many of their patients were self-medicating with illicit cannabis, whereby the general sentiment was that they were comfortable for their patients to do so, especially if the clinicians could notice beneficial effects, but that this was not a sufficiently compelling justification for them to prescribe.

> *"The problem we've got here is that the patient might have a diagnosed illness, a properly diagnosed illness and so forth, but they have self-medicated and then want that to continue officially—I think that is a real dilemma."*
>
> **Dr Richard Braithwaite**
> **Psychiatry**

There was, nonetheless, an acute awareness of the disadvantages of illicit cannabis, namely, the legal implications, uncertainty over the purity or contamination of the product, the inconsistency of strains, the need to purchase from suppliers on the illicit market and the dosage.

Mode of Administration

Challenges and uncertainties surrounding the dosage and modes of administration for CBPMs were raised by many of the clinicians, who explained how both themselves and their patients would likely feel more comfortable prescribing medical cannabis in pill form.

This is the most conventional mode of delivery for medication that facilitates the concentration of each compound and a known dosage to be consistently delivered.

> *"The more conventional delivery perhaps the more comfortable many people would be. And that's true of anything. There's a cultural element… but I don't think that's a major issue, provided you can be confident that it's an acceptable route of delivery and it's delivering consistent dosing."*
>
> **Dr Richard Davenport**
> **Neurology**

The vast majority of licensed medical cannabis is prescribed in a spray or oil form. However, concerns arose over the mode of administration for medical cannabis when in flower form, where the most familiar and traditional form of administration is via smoking or vaping the product, which clearly presents multiple issues for clinicians.

> *"I think doctors would always prefer something that's characteristics are very tightly defined, delivery is very tightly defined, but it doesn't have to be a tablet, but I think putting the herbal product into a vape is probably not going to be medical enough."*
>
> **Dr Rick Anderson**
> **Psychiatry**

It is well established that smoking and vaping are detrimental to health, and particularly the mouth and lung, even though the full impacts of vaping are not yet known. Therefore, the clinicians were generally opposed to patients smoking or vaping their cannabis, even though these are the methods through which most people are currently self-medicating. A few clinicians also outlined the strong association between smoking cannabis

and its recreational use, which introduced unwanted risk by blurring the boundary between medical and recreational use.

> *"If you're smoking or vaping it, you're immediately equating it to how it's used in the street sort of thing. Whereas in a tablet it is obviously, that's what we do."*
>
> **Prof. Peter Whorwell**
> **Gastroenterology**

> *"I do think, amongst other clinicians, it is a worry and it is a concern that it's not a tablet...if you were to prescribe it as a bud or as a flower, there's a connection with the illicit use through that very physical encounter that doctors and the public have, just walking down the street."*
>
> **Dr Pramod Mainie**
> **Neurology**

> *"From my point of view, the medicalisation of it would require it to be made available, either injectable, tablet or syrup. Vaping is too much like through a bong, and it also has implications for lung health. So I'd be worried about vaping, inhalation."*
>
> **Dr Justin Basquille**
> **Psychiatry**

It was noted, however, that the risk–benefit ratio should be assessed according to each individual patient's circumstances, along with the standard of care they are currently receiving.

> *"I suppose it depends, if someone has very bad pain and the quality of life is rather low, I think you have to have a risk–benefit ratio with regards to this kind of thing. Not all drugs are 100% safe but it's a matter of finding something which gives you more benefit than harm."*
>
> **Dr Adam Woo**
> **Pain**

A key issue raised was the significant challenges of controlling or standardising the dose of cannabis when smoked or vaped. The clinicians highlighted the importance of being able to tightly control the dosage when prescribing medication, and that any inability to do so is incompatible with the existing medical model. This was especially relevant to the neurologists, who explained that the smallest of variations in dosage could have significant implications for the patient's health and wellbeing.

A range of concerns and uncertainty were also raised regarding the bioavailability of the desired compounds when administered in different form.

> *"With tablets it is pretty predictable what somebody is going to get, what the pharmacokinetics, the pharmacodynamics, the body's response to that will be. Inhaling something, it's difficult to know how much of it somebody is going to get, the issue is with regards to bioavailability."*
>
> **Dr Rick Anderson**
> **Psychiatry**

> *"I think it's more about standardising it, and of course that's the trouble with plant based: you can't standardise it…"*
>
> **Dr Stephen Ryder**
> **Gastroenterology**

"For epilepsy a small variation in dose can be huge and can cause breakthrough seizures. So we always try to keep the dosing as stable as possible, so if you are getting variability in the absorption, you're getting variability in the actual form of cannabis that is being taken, you're going to get huge variation in dosing, and what we know with epilepsy is that taking a drug erratically is often as harmful as not taking it at all…I think if I were to prescribe cannabis, it would have to be in some way that you can give a very accurate, measured dose and you could know exactly what the person was taking each time."

Dr Chris Derry
Neurology

"Having a standard dose is essential, we've got to get this right as otherwise cannabis is unpredictable and we do not know the harms and benefits. Cannabis must be standardised to be brought into the mainstream, otherwise it will continue to be used in a pseudo-recreational way. …This will massively increase the willingness to prescribe as it is how medicine is currently practised."

Dr Euan Lawson
General Practitioner

Overall, there was a general sense of uncertainty regarding the efficacy, safety and practicality of different modes of administration, with these unknowns eroding most clinicians' willingness and confidence in prescribing cannabis. Solutions included the suggestion that pharmaceutical companies develop standardised forms such as patches, gels, pills and oil extracts, and clearly further research is necessary to explore the different forms of administration.

"I think that if you were to use it, there should be some edible form. But you need to have the proper studies to show what the kinetics are. I know some of the kinetics for street cannabis is done in smoking, but I don't really know what's the kinetics if you eat it, which you could argue would be a nicer way to do it, but what impact it has on the liver."

Prof. Ley Sander
Neurology

Costs and Funding

The cost of the licensed medications was raised as a significant barrier for many clinicians, and especially the neurologists whose practices could not absorb the considerable costs of prescribing cannabis to many patients for any reasonable length of time.

"…it's costing upwards from £35,000 per patient per year—which is an absolute disgrace…what they want to do is have us roll this out at exorbitant cost and prescribe the medicine with no evidence to back it up regarding safety or efficacy..."

Prof. John Leach
Neurology

Even looking beyond currently licensed medicines to medical cannabis available outside the NHS, the aforementioned excessive cost creates a two-tiered system that potentially excludes a significant number of patients according to income, since the majority of people simply cannot afford a private cannabis prescription. This moderates private clinicians' decision to even mention medical cannabis as a treatment option to avoid disappointment, since they know that for the vast majority of patients it is economically inaccessible.

> *"The majority of my work is on the NHS, so I can't anyway. Maybe 10% of my patients, because I live in quite an affluent area, might have the financial means to pay for it themselves but the majority don't, therefore, it's probably cruel to even mention it as a potential treatment."*
>
> **Dr W Allister Dow**
> **Pain**

When combined, these factors drive many clinicians to concede that it is simply easier to refer their patients to a private cannabis clinic where prescribing is more likely and the costs are reduced, although these ultimately must be borne by the patient.

Cannabis Exceptionalism

A general point regarding medical cannabis was that it currently sits outside of mainstream medicine, with many clinicians feeling that its proponents were pressing for it to be treated distinctly from other drugs.

> *"This highlights the difficulties with it being a 'cannabis clinic' it would be better to use cannabis as part of a wider intervention with the intervention not just being about cannabis. What we have now with the UK clinic model is an inherent bias for cannabis working before testing it out, the industry has decided it works and is now looking for conditions where it can be proven."*
>
> **Dr Euan Lawson**
> **General Practitioner**

> *"I think it sounds a bit absurd…the idea of a single drug clinic, especially when it's not necessarily even within one particular medical specialty."*
>
> **Dr Richard Braithwaite**
> **Psychiatry**

Some clinicians felt that the push for cannabis to be treated differently from other medications contributed to the media's framing of clinicians as unsympathetic and overly conservative. In reality, they believed that they were treating cannabis as per any other drug and exercising caution in light of the absence of evidence, guidance and infrastructure to prescribe.

> *"You must understand the potential risks you run if you decide to treat it entirely differently from any other drug. It's nothing to do with doctors wanting to see cannabis fail, or deny cannabis to their patients, which is how we're sometimes portrayed. Some of the high-profile child epilepsy things, they're portrayed in a particularly unsympathetic and difficult manner that is really evil doctors trying to deny drugs to patients, risking their lives, which is very easy to write in a newspaper but is nonsense."*
>
> **Dr Richard Davenport**
> **Neurology**

Then, the calls for medical cannabis to be treated differently from other drugs undermined its credibility in the eyes of some clinicians, who felt that if it was as effective as the claims proposed, it would not be necessary to bypass the evidential and regulatory standards in place for other new medications. Even if they were optimistic about its potential, the majority of clinicians still thought medical cannabis should not be treated any differently from other medications.

> *"That all has to come down through clinical trials, and I do worry a little bit that cannabis has been marketed as such a great thing and it's always doing it the other way round compared to most medicines, where most medicine companies develop it and do the studies and say, "This is the indication", whereas [the cannabis industry] is saying "this is the medication" and it's for everything. It's not found in a specific area, which again, worries me a little bit. It does worry me, the way it's been developed and slightly pushed."*
>
> **Anonymous**
> **Gastroenterology**

Most clinicians did not want to practise in a cannabis clinic where the answer to any indication would generally be to prescribe cannabis, instead indicating a desire to be able to prescribe medical cannabis from their existing practices.

> *"…obviously if you go to that clinic, you're going to attract people who want cannabis without any evidence. So, I am slightly concerned about these clinics and the bias and the motivations that are behind the people who run them"*
>
> **Anonymous**
> **Gastroenterology**

Some clinicians voiced frustrations with the pressure to continue prescribing medicines initiated in cannabis clinics, whereby patients may come to clinicians having already been on a private CBPM prescription and therefore the NHS clinician has little choice but to continue the treatment. The high cost to the NHS of continuing these prescriptions was also raised.

> *"Put it this way: I'm an enforced prescriber of medical cannabis. Patients will come to me and they're already on it and we then have to just bite the bullet and continue the prescription."*
>
> **Prof. John Leach**
> **Neurology**

Conclusion

It was evident that the clinicians perceived a reputational risk and stigmatised cannabis as a medicine either consciously or subconsciously, which appeared to be exacerbated by a general lack of knowledge. Many of the barriers to prescribing medical cannabis stemmed from its uniqueness as a medicine and the historical prejudice. Consequently, many clinicians cited the concern of prescription requests for the ultimate purposes of recreational use.

Factors such as the mode of administration contributed to hesitancies, given the unconventional means of delivering the drug combined with the lack of measured, consistent and standardised dosing. The clinicians sensed a drive within the industry to treat cannabis differently to other medications, undermining its credibility and thus creating a resistance to prescribing

Chapter 6: Implementing Solutions

There are clear and obvious limitations to the current UK medical cannabis prescribing system, as illustrated by the lack of prescribers. Through the views expressed by the clinicians in Chapter 5, the barriers largely centre around a lack of evidence on efficacy and safety, and insufficient governance on cannabis prescribing, along with specific concerns regarding the use of cannabis as a medicine.

After acknowledging the concerns of clinicians, Volteface began to explore the existing solutions and innovative steps currently being taken in the industry. We spoke to representatives from a range of organisations (n=11) that are seeking to address the issue of medical cannabis prescribing, and how this can be achieved more effectively to ensure that patients' needs are met.

There is a growing body of work taking place to address these concerns through helping to adapt and integrate cannabis prescribing into mainstream healthcare. This chapter explores some of the solutions under development to address clinicians' concerns and their reluctance to prescribe.

Prescribing outside the clinic model

Many clinicians voiced concerns and confusion over the current prescribing system for medical cannabis. Although the current model has enabled some, albeit limited patient access to date, the clinicians shared their reservations around joining or working with a clinic that offers a single pharmacological agent—a model that does not exist for other prescription medicines in the UK today.

This has been a limiting factor, with cannabis-interested clinicians not wanting to work in a clinic with such a narrow prescribing frame. Given the limitations of this model, there is a need to implement more straightforward and effective governance practices in existing private-prescribing environments. The research we carried out suggests that clinicians would benefit from being able to prescribe outside the auspices of the cannabis clinic, and that the lack of opportunities for independent prescribing may be contributing to the low number of cannabis-prescribing outcomes.

One solution would be to offer an easily accessible governance platform containing detailed information on evidence-based products that have clinical rationales for specific indications. The lack of knowledge amongst clinicians regarding the practicalities of prescribing and general information necessary to feel familiar with cannabis also needs to be addressed. This could be achieved through high-quality education and learning resources that clinicians can access to learn more about medical cannabis, its indications and, more specifically, how to actually prescribe it.

Sana Healthcare is a licensed medical cannabis importer and distributor focused on clinician-focused prescribing solutions, whose mission has centred around extending accessibility to cannabis prescribing outside of the parameters of cannabis clinics. In line with the concerns raised by clinicians throughout this report, Sana Healthcare draws medical cannabis out of the periphery as a medicine in the UK healthcare system without exceptionalism.

With this in mind, Sana Healthcare's approach focuses on enabling clinicians to prescribe CBPMs appropriately, whilst acknowledging that these products cannot and should not always be the optimum prescribing solution. This means creating a model where a range of treatment options are available including, but not confined to medical cannabis prescribing.

"We're looking to solve the persisting limitations of the cannabis industry through technology and data collection. Sana is primarily a clinician-focused company, working to understand their pain points for prescribing cannabis products as we recognise this is necessary to effectively kickstart independent prescribing."

Arjun Rajyagor
COO at Sana Healthcare

Sana Healthcare has developed *Script Assist*™, an integrated governance platform to support clinicians prescribing medical cannabis. Explanations are provided for every stage of the required governance and risk management measures, along with practical processes of issuing a prescription and facilitating access to a multidisciplinary team. With a focus on clinical governance and a multidisciplinary perspective, *Script Assist* aims to reshape the sector's approach through supporting decision-making and the management of clinical risk.

With a lack of governance highlighted as a key barrier by clinicians, the *Script Assist*™ platform is a solution by streamlining the process and addressing the lack of understanding regarding the practicalities of prescribing expressed by the medical community.

"The platform contains information, data and guidelines on what is required for a clinician to feel comfortable prescribing cannabis. It supports them through the whole process."

Arjun Rajyagor

Script Assist™ allows products to be directly dispensed to patients with clear guidance surrounding the evidence of efficacy in a given indication, as well as the dose, frequency and mode of delivery.

It also offers an integrated supply chain, meaning that the patient is far more likely to receive the prescribed product in a timely manner, as opposed to the issues that can arise through current arrangements.

There is also a patient-facing application to assist throughout the process, from locating an appropriate specialist, to establishing and recording goals and outcomes in partnership with their treating clinician. The platform facilitates ongoing data collection to help prescribers review appropriate courses of action in terms of managing the treatment regime, including whether medical cannabis should continue to be prescribed as the optimum treatment option.

Sana Healthcare's model is working towards providing clinicians the confidence in safely prescribing for their patients.

Clinicians and patients are key stakeholders in medical cannabis prescribing in the UK, and therefore it is imperative that they are empowered to ensure that the right people get the right medication at the right time.

"We are bringing in a framework with a structured approach to cannabis prescribing. This allows clinicians and patients to keep track of progress against very specific goals to understand whether the medicine is working. A huge part of Script Assist is the communication between the patient and doctor.

It's really important to stress that this is not a platform for a cannabis company. It's independent and unbiased for clinicians to understand how their patient is doing and collect real-world evidence in the process.

At Sana we recognise the need to treat cannabis like any other medicinal product to ensure widespread acceptance and uptake.

This is why efforts need to be focused on expanding prescriptions in the private sector with cannabis being an unlicensed medicine. From a regulatory perspective, Sana is not looking to change prescribing, seeing as it is an unlicensed specialist medicine, it should continue to be prescribed via the specialist route."

Arjun Rajyagor
COO at Sana Healthcare

Indication-specific products

The lack of indication-specific evidence for products was a concern raised by many clinicians, who explained that cannabis is not being prescribed in a specific and targeted manner. There are, however, products offered for specific indications in treating those specific indications.

Tikun Olam is a leading medical cannabis brand and research organisation, dedicated to a data-led approach, across various indications, including paediatric epilepsy,[58] gastroenterological disorders,[59] dementia,[60] autism, and cerebral palsy movement disorder.

Dr Lihi Bar-Lev established Tikun Olam's research department 15 years ago with the aim of supporting patients and conducting clinical studies in a standardised manner. She has now published 23 studies.

Through her extensive research into cannabis, Dr Bar-Lev acknowledged there are several considerations when working with cannabis that need to be accounted for, such as finding the correct balance between CBD and THC.

"CBD doesn't act like THC in a single application. You have to consume it repeatedly for 1 to 2 months to see the effects. Whereas with THC you see an effect very quickly - especially for symptoms like pain, appetite and sleep disturbances. Differences in the way CBD and THC acts requires patience from the patient. Treatment can thus be quite frustrating on CBD for both the patient and physician. THC is used more for symptoms that have a direct effect on the body (tremors, spasticity, pain) whereas CBD is a more longer-term effect.

THC is more for breakthrough pain."

Dr Lihi Bar-Lev
Head Researcher at Tikun Olam

She also noted that it can be complicated for clinicians studying cannabis, given its complex structure.

"Naturally, hesitancy for clinicians toward cannabis treatment can comes from a lack of knowledge across a few parameters. The plant itself is confusing in its structure and confusing when you are dealing with many molecules. Physicians are used to one molecule, binding to one receptor, activating a single mechanism of action to a response. For me, this is what the beauty of cannabis is and what makes it so amazing as it acts on so many different things. And because of this, the efficacy of the drug link to additional benefits coming from the use of cannabis. We can see this as a 'ripple effect' with an improvement in quality of life.

But for a physician, it is complex, especially needing to understand the different compounds of the plant - cannabinoids, terpenes, flavonoids - only in the cannabinoid group there are over 112 different ones identified structurally."

Dr Lihi Bar-Lev

Bar-Lev said that clinical trials are the only way in which confidence and safety in cannabis' use as a medicine will be established. The results are promising, including a reduction in opioid medication.[61] A multitude of issues need addressing to ensure that clinicians become comfortable prescribing cannabis, primarily THC's psychoactive status, which is a significant barrier for both clinicians and patients.

"The psychoactive effect can be frightening, something that needs to be handled and talked about. However, this is solved through titrating the patient through a slow, gradual increase. This is of course another complication of titration - there isn't one acceptable dose. If we take a paracetamol pill, two individuals will receive approximately the same dose with a similar reaction and same time. With cannabis, it isn't like this - each patient starts from a very low dose to avoid side effects. In order to avoid this, we have to start very low as some will respond to such a low dose.

This increases until some kind of relief is felt, or until you experience some kind of side effect tampering down to the appropriate dose. This is quite a unique effect to cannabis - titrations means it takes longer to identify the correct dose which means the research is more straining, time consuming and difficult to conduct - monitoring - a significant amount of the study is focused on titration and it costs more.

"We are seeing progress in the way cannabis is being accepted, the question whether it will be properly accepted lies in how cannabis is presented, there is so much evidence gathered and it's not like other medicines. In order for clinicians to come with us, they need to receive the knowledge as they are used to - double blind placebo controlled trials, evidence-based medicine. If it is evidence-based, it is easier for them to be on board and that is what we give them."

Dr Lihi Bar-Lev

Little Green Pharma (LGP) was first licensed to cultivate and produce medical cannabis by the Australian Federal Office of Drug Control in April 2017. They have received a good manufacturing practice (GMP) licence and currently offer cannabis-based products in the form of oil and flowers, producing for domestic use and international export. Citing the industry-wide distrust amongst clinicians when novel medicines have not undertaken clinical trials Dr Leon Warne, Head of Research, reported that LGP have utilised a methodology whereby their products are validated and peer-reviewed by university academics. This method tends to be quicker than clinical trials, although it still involves a lengthy process.

Dr Warne viewed general practitioners as being more likely to prescribe medical cannabis over specialists, since they are better informed about the patient's condition and familial medical history, while representing most patients' first point of access. He also commented on their greater ability to conduct routine follow-ups, which is necessary considering that medical cannabis is a novel prescription.

"The GP population who deal with chronic disease on a daily basis, who manage patients, who are the continuity and care between multiple specialists are the types of clinicians…because they have a good understanding of all of the factors of a particular patient, [and] are likely to take on new [medicines] when other treatments have failed, like medicinal cannabis to improve the quality of life of their patients."

Dr Leon Warne
Head of Research, LGP

The overcomplication of cannabis prescribing was raised as a concern for Dr Warne, where he considered there to be sufficient literature to support dosing. When products are manufactured at the GMP level, variabilities in medicinal quality are greatly diminished. Dispensaries, therefore, were considered a hindrance to clinicians prescribing cannabis, who perceive this distribution medium as less legitimate and who may not have the time or motivation to inform themselves of the counterarguments. He noted that established data already exists on polydrug interactions with medical cannabis, as well as adverse reactions and dosing.

"There needs to be digestible education that accommodates the Westernised real-word evidence-based and clinical trials, as well as the more alternative paradigms."

Dr Leon Warne

In partnership with the University of Sydney, LGP is currently undertaking QUEST:[62] the largest longitudinal, observational study in the global history of medical cannabis involving nearly 3,500 patients. Preliminary findings indicate statistically significant results with an improvement in quality of life, which Dr Warne spotlighted as a quantifiable measurement of success, particularly given that patients could have comorbidities or be taking multiple medications. This metric was considered a crucial component in considering comorbidities and chronic pain, given the longevity of the conditions and their impact on daily life. These factors render quality of life a pivotal metric for encompassing the patient as a person, and how they interact with the healthcare system.

The notion that cannabis research is difficult to conduct is a fallacy according to Dr Warne, who argued that there are opportunities to conduct credible studies even with lower budgets. Alongside their longitudinal study, LGP sponsors three PhD research students, thereby creating evidence to support their products through an annual investment of $28–30,000 per clinical student, as opposed to investing $28–30 million in a clinical trial. Teachers, hospitals, and academic institutions are often keen to engage with industries on research projects.

Below are several examples of products offered for specific conditions with a degree of data behind them, providing reassurance for their use in those specific indications.

Crohn's Disease

A double-blind placebo-controlled study examined the efficacy of THC-rich cannabis as a treatment for 21 Crohn's disease patients, where the treatment arm was associated with a decrease in disease activity in 10 of 11 subjects in the cannabis group, compared to 4 of 10 on placebo. Furthermore, remission was achieved in 5 out of 11 subjects in the cannabis group.[63]

Another double-blind randomised placebo-controlled single centre trial examined the impact of oral cannabis oil on clinical and endoscopic outcomes in mild-to-moderate Crohn's disease,[64] where 56 patients received oral cannabis oil with 160mg/40mg CBD/THC or placebo for eight weeks.

The treatment was shown to significantly reduce the disease activity index and improve quality-of-life ratings, whereby a daily dose of CBD-enriched oil improved pain, mood, sleep, appetite, satisfaction and wellbeing. No patients withdrew from the study due to tolerability issues.

These RCTs show significant promise for the use of cannabis oil to treat Crohn's disease.

Intractable Paediatric Epilepsy

Retrospective research from four paediatric epilepsy units in Israel shows evidence for CBD-enriched medical cannabis through a cohort of 74 children.[65] The medication formula contained CBD and THC at a ratio of 20:1, with half the patient cohort receiving Avidekel (Tikun Olam). The dose titration determined regulatorily according to seizure response and any side effects reported during clinic visits.

Assessing seizure frequency based on parental reports, medical cannabis had a positive effect on the seizure load, with the majority of the children (89%) treated for at least three and an average of six months having a reduction in seizures. Improvements in behaviour were also observed, along with enhanced alertness, communication, motor skills and sleep ratings.

An aggravation of seizures was reported in 7% of children, leading to the withdrawal of medication, where reactions included somnolence, fatigue, gastrointestinal disturbances and irritability. No children displayed allergic reactions, with the side effects being temporary and no different to other antiepileptic drugs. This study was part of a case series without any control group, although the patients were well known to the treating clinicians.

The study demonstrated promising results for this particular cohort of difficult-to-treat patients.

Paediatric Motor Disorders

A prospective study assessed the efficacy, safety and tolerability of medical cannabis in children with complex motor disorder over the course of five months.[67] Two 5% CBD-enriched formulations of the cannabis product Avidekel (Tikun Olam) were compared, one with a CBD:THC ratio of 6:1, and the other of 20:1.

Statistically significant improvements in spasticity and dystonia, sleep, pain severity and quality of life were found in the total study cohort, regardless of treatment assignment. Out of the 25 patients, five were withdrawn from the study due to worsening seizures, behavioural changes and somnolence. There were no interactions with other medications.

This pilot study suggests that CBD-enriched oil with CBD:THC ratios of 6:1 and 20:1 may be effective in treating children with complex motor disorders.

Although the small sample size and the lack of a control group are problematic factors limiting the conclusions that can be drawn, the findings are nevertheless promising.

Chronic Refractory Pain

An observational study examined the effectiveness, adverse events and quality of life in patient-reported outcomes in those prescribed a cannabis oil formulation for chronic pain.[67] This real-world evidence was assessed alongside standard care to explore the safety, tolerability and effectiveness of pharmaceutical grade medical cannabis oil (LGP Classic 10:10).

Pain impact scores were significantly reduced across the cohort of 151 patients, with half the patients benefiting from improvements in sleep and more than one-third reporting reduced fatigue. Overall, there was a positive effect of 10:10 oral medical cannabis oil on pain, with a reduction in pain intensity that did not quite reach statistical significance. This group of patients had not previously responded sufficiently to standard of care treatments (including opioids), and therefore the results are of particular interest.

The need to conduct further clinical trials

A crucial barrier to introducing CBPMs onto the market is the need for academic clinical trials. Life science consultancy firm Knowde Group Inc. was established in Canada to assist enterprises with the process from drug development to commercialisation, and also operate in the UK. Their firm seeks to connect the different organisational bodies to improve the research and output of life science enterprises, and to reduce the information asymmetries between them.

Physicians are hesitant to prescribe CBPMs, primarily due to the lack of completed clinical trials that are necessary in order to fully understanding the potential polydrug interactions, long-term patient side effects, and the genetic variability in the patients' and their family's medical histories. The clinical trials submitted for approval to date are often either real-world evidence or flower-based, both of which would be denied by regulators and jurisdictions. Therefore, it appears that there is a disconnect between biotech firms, investors, regulatory bodies and governmental bodies, with resources wasted as a result.

Knowde Group seeks to bridge these information gaps in order to guide companies through the research and commercialisation processes. They consider cannabis to be more nuanced because of its botanical nature, thus encouraging a shift away from raw active pharmaceutical ingredient formats towards more traditional, standardised pharmaceuticals. For example, a stable drug delivery mechanism is crucial to the successful approval of clinical trials (i.e. using tablets over flowers), as well as indicating specific disease states targeted by the cannabis-based product.

Investors are also more likely to be attracted to innovative technology such as device and drug combinations. Further innovation is therefore needed from biotech firms in order to find novel solutions for integrating cannabis-based products and technology. Knowde Group acknowledged that numerous cannabis-based biotech producers are led by individuals who are not pharmacologically trained and lack clinical experience.

A company doing similar work and showcasing alignment to a data-led approach in the industry is Cymra Life Sciences. Cymra are developing condition specific products backed up with clinical data that is following strict clinical protocol to obtain mainstream pharmaceutical approval. They have a particular interest in chronic pain given the unmet need with no current medicines approved by most worldwide regulatory bodies for this indication. Cymra are running a clinical program for a uniquely formulated Australian made full spectrum cannabis oil targeting chronic pain and have completed a phase 2 dose ranging study for efficacy with final results imminent. Whilst still awaiting publication, preliminary results look highly promising for moderate to severe chronic pain.

> *"If we want acceptance of medicinal cannabis products, we have to do serious clinical trial work to put data in front of physicians and agencies. This is the only way to convince regulators and clinicians to prescribe our products through the regular channels. This must be done using a well-established method, according to good clinical practice and presented to physicians and agencies in a clear manner.*
>
> *If you look around the universe of medical cannabis data, there is quite a lot of it. However, most of the data is of relatively low quality compared to other registered drugs. Observational data shows that indicatively cannabis can potentially help with chronic pain, however observational data alone does not meet the regulatory approval criteria and we must follow the standard that our regulatory agencies are setting."*
>
> **John Montgomery**
> **Executive Director of Cymra Life Sciences**

Innovative mechanisms of dosing and administration

Israeli-based Syqe are at the frontier of cannabis technology, having designed a combined medical device, namely, an inhaler for standardised clinical treatment.

The inhaler utilises cartridges containing 13.5mg of raw medical cannabis with 20% THC. Patients can choose doses based on their daily needs and activities, with the inhaler's core goal being to balance pain relief and daily functioning.

Vogel referenced a consistent theme within the cannabis literature, where during treatment patients will experience adverse effects such as psychosis, which are central to claims against the widespread prescribing of medical cannabis. The broad range of cannabis production methods do not produce standardised products, meaning that patient efficacy and treatment can vary significantly depending on which terpene or CBD:THC ratio is created. It is believed that high THC levels are damaging to long-term mental health, which has remained a pervasive barrier amongst clinicians, particularly in the NHS. Nevertheless, dosing concerns are addressed by Syge's inhaler device: as the cartridges contain standardised cannabis doses, patients are less likely to dose incorrectly as they can monitor output, and they can share consumption data with healthcare professionals through their smartphones.

Vogel claimed that Syqe have developed a "new therapeutic window" of microdosing with high efficacy for pain relief, following a series of real-world evidence trials conducted on patients using their inhaler, where 92% of patients reported improved quality of life, and 58% of those using opioids reported a reduction in use.

> *"You'll hear it all the time from patients that will tell you, "One month it helped me, one month it didn't. One day I come out of work feeling energised, one day I can't get out of bed".*

> *They're on a clinical rollercoaster all the time between efficacy and adverse effects. For chronic patients, that's not a way of life—they need stability. They need a treatment they can trust, where they know what will happen, and build their lives upon that."*
>
> **Jacob Vogel**
> **Director of Global Sales & Business Development, Syqe**

Australian-based and Singapore-listed iX Biopharma is a pharmaceutical company with expertise in drug delivery that has developed a novel proprietary sublingual delivery technology called *WaferiX*. *WaferiX* is particularly suitable for medical cannabis, creating new dosage forms. With its roots as a traditional pharmaceutical background as opposed to being a cannabis company, iX Biopharma places significant emphasis on the importance of its clinical trials, as well as the quality and consistency of its products.

IX Biopharma's technology is novel, patented and non-invasive. The delivery mechanism of WaferiX is unique in having a porous microstructure, as opposed to clinging or adhering to other substances, meaning that when placed under the tongue it dissolves in 15–20 seconds, allowing the product to be absorbed in the sublingual mucus. The product's structure does not lead to a large amount of saliva being produced by the patient due to its rapid dissolution, thus being particularly suitable for patients with dexterity issues and difficulties in swallowing.

Medical cannabis products typically struggle with poor bioavailability through delivery mechanisms such as tinctures and oils. What is unique about the *WaferiX* approach is that it avoids the gastrointestinal tract, entering the blood system quickly, and thus requiring less of the product. iX Biopharma's CBD wafer is faster acting due to the novel delivery mechanism. Pharmacokinetic data for *WaferiX* demonstrates rapid absorption and a faster onset of action; it is also dose proportional, less variable, safe and well tolerated.[69]

Peer-to-peer support and education amongst clinicians

The lack of education and awareness that tends to prevail amongst clinicians was cited as a substantial barrier to confidence in prescribing cannabis. However, there are several educational and community-based initiatives to support clinicians through the prescribing process.

Creating a community to support clinicians

Hannah Deacon and Prof. Mike Barnes founded the Medical Cannabis Clinicians Society (MCCS) on the day the UK law changed in 2018. The society was created to support education, training and mentoring for any clinicians interested in learning about medical cannabis and how to prescribe it. Their work has focused on educating clinicians through events, informative guidelines and creating a network through which advice can be sought via peer-to-peer support.

Awareness-raising is at the heart of bringing more clinicians on board, providing basic knowledge and information about cannabis. According to Prof. Barnes, while a knowledge base helps to provide reassurances in terms of prescribing, such education must be delivered in unison with mentoring and support.

Deacon and Prof. Barnes believed the core issue is clinicians' fear of the unknowns surrounding cannabis prescribing, and their reluctance to take responsibility for prescribing an unlicensed plant medicine. Education and peer-support through the MCCS is therefore a means to address this gap and support cannabis prescribing, where appropriate.

Awareness-raising amongst general practitioners

Dr Leon Barron is a general practitioner who has been actively involved in the field of medical cannabis since the change of the law in 2018. Upon realising the significant benefits that cannabis could offer in UK clinical practice, he established the Primary Care Cannabis Network. Dr Barron's aim was to share learnings with other general practitioners to raise awareness and focus on the scientific benefits of cannabis.

Since general practitioners are increasingly asked about cannabis-based products and CBD by their patients in routine consultation, stigma is "definitely diminishing", whereby in Dr Barron's view, *"I would say GPs are probably more open to it, if presented information correctly", while in terms of alleviating fears around prescribing, "the reality is that cannabis prescribing has a lot more knowns than unknowns when compared to the illicit market—regulating and standardising products for medical use is massive".*

Dr Barron echoed the need to support independent private prescribers outside of cannabis clinics, as *"the model we have currently does not move the conversation forward. Clinicians want to prescribe it within their own, established practice."*

Professionalising the industry through education

There are a number of educational platforms and courses offered to help educate healthcare professionals on the use of medical cannabis.

With a background in building educational platforms in various industries and realising there was a lack of such a platform in the medical cannabis domain, in 2019 Ed Koyuncu established Plantific, an accredited plant science educational platform.

As opposed to a cannabis company, Koyuncu highlighted that Plantific is a professional education company that seeks to put forward unbiased, trustworthy content for the sector. He holds expertise in learning objectives, assessment criteria and developing courses with a track record for achieving good quality assurance in diverse fields. Given the interdisciplinary nature of cannabis, platforms such as Plantific need to project the right tone, advocating for the dissemination of objective information, with an important emphasis on the building of credibility and trust.

Conclusion

There is a significant amount of innovation already unfolding to address some of the key issues raised by the clinicians in this report, with this chapter exploring a number of the solutions that exist and serve to build trust and credibility in the context of CBPMs.

As outlined by Sana Healthcare, alternatives do currently exist to prescribe outside of the cannabis clinic model through platforms such as Script Assist that provide clinicians with greater flexibility and data on the patient's usage. Initiatives like this can help to normalise CBPMs into mainstream practice, rather than being left to the fringes of healthcare prescribing.

The lack of indication-specific products with reliable evidence was one concern raised amongst clinicians. However, companies such as LGP and Tikun Olam are addressing this issue through developing and researching products for specific conditions with a particular level of supporting evidence, thus helping to build assurance amongst clinicians.

Similarly, with the lack of high-quality clinical trials a major obstacle for the acceptance of medical cannabis, Knowde Group and Cymra Life Sciences demonstrate that effective and credible trials of this nature are possible for botanical medicine, with many already underway.

Innovations developed by groups such as Syqe and iX Biopharma are offering solutions to the limitations of administration and dosing that clinicians encounter in terms of prescribing confidence.

Through developing consistent, metered dosing with fast onset and high bioavailability, such concerns can start to be allayed.

Lastly, awareness-raising in the clinical community was consistently raised as something clinicians would benefit from, with this report identifying active education courses and peer-support networks that are already helping clinicians navigate and learn about the complexities of medical cannabis through initiatives such as the Medical Cannabis Clinicians Society and the Primary Care Cannabis Network. Meanwhile, educational platforms such as Plantific are helping to professionalise the sector through their provision of unbiased and credible information.

Nevertheless, despite this momentum more progress is required to broaden clinicians' access to medical cannabis information in terms of the practicalities of prescribing. Solutions to many of the challenges cited by the clinicians in this report do exist. Therefore there is a need to bridge the gap between clinicians and the medical cannabis industry, to formulate a safe means of expanding access to the CBPMs, as and when appropriate that allays clinicians' concerns and provides increased opportunities for patients to benefit from novel treatments for their chronic conditions, while eroding the stigma and resistance that prevails in the professional and regulatory bodies.

Chapter 7: Conclusion: Moving Forward

There are an estimated 1.4 million individuals using cannabis for medical purposes in the UK, but less than 15,000 of these use legally prescribed products. Known Unknowns thus presents an analysis of the shortcomings of medical cannabis as a CBPM in the UK, shining important light on the reasons why clinicians are reluctant to prescribe medical cannabis. The report explored challenges relating to efficacy, research, regulation, education and accessibility.

According to the interviewed clinicians, limited clinical engagement to expand access has been a key roadblock within the current regulatory environment, leaving cannabis on the fringes of medicine as a largely unexplored field.

The research has demonstrated a clear disconnect between clinicians' perceptions of medical cannabis and the reality of the R&D work already taking place in the industry, as well as a mixed consensus on clinicians' stance towards medical cannabis, stemming from a lack of education and ambivalence towards the drug.

This report has sought to bridge that gap, shining a light on clinicians to better understand their perceptions of cannabis. A significant component of clinicians' hesitancy to the drug arises from insufficient knowledge, lack of exposure and fear of the unknown. Known Unknowns has adopted a clinical approach to the issue, proposing that the only route to bring medical cannabis into the mainstream framework is through understanding and addressing clinicians' current concerns regarding.

The clinicians also voiced a lack of understanding of the current infrastructure for prescribing cannabis, along with concerns over their reputational damage should they wish to do so.

Many of the barriers to clinicians prescribing and embracing CBPMs as a treatment option stem from its uniqueness as a medicine and the associated historical stigma. This has led to concerns surrounding legitimate medical use, as well as the close association with recreational use and certain modes of delivery.

It is clear that CBPMs are no panacea, with Known Unknowns calling for cannabis to be treated as per any other medicine and to feature as merely another tool in the clinicians' formulary. Private clinicians should certainly not feel under any obligation to prescribe CBPMs, but rather have the confidence to prescribe medical cannabis (where appropriate), alongside and integrated within the broader care that they offer their patients.

One of the largest discussion points amongst the clinicians was the hesitancy towards prescribing CBPMs due to a lack of evidence, and particularly in terms of the type of evidence, citing the need for high-quality evidence in order to feel confident when prescribing such treatments. In particular, the insufficient number of RCTs was perceived as one of the most significant limitations that leads to prescribing hesitation.

While promoting evidence-based practice using the scientific approach is essential, we should remain mindful that evidence and data sit within a spectrum. Therefore, non-RCT studies should not be disregarded as a matter of course, as such responses limit patient access to new and innovative medicines.

Dr David Sackett, a pioneer of evidence-based medicine, rightly pointed out that while RCTs are understandably the gold standard and a necessary pillar of evidence, [70] there are others pillars of medical evidence that also need to be considered.

If we are to broaden our evidence-based lens for other medicines, then why should cannabis be any different?

> *"Evidence-based medicine is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions.*
>
> *…some questions about therapy do not require randomised trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted. And if no randomised trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there."*
>
> **Dr David Sackett**

It is important that clinicians adhere to this guidance and not restrict themselves, and therefore while recognising RCTs as the gold standard, they should also acknowledge the other forms of evidence that can be employed to justify the use of CBPMs in the interim.

This report has focused its efforts on identifying the roadblocks within the existing framework since the rescheduling of cannabis-based products for medical use in 2018, and thus avoided any recommendation for further policy change. The reason for this is simple. As the existing regulatory framework allows for private prescribing, we need to better understand why access remains so limited, and therefore rather than calling for further changes to policy, the focus must be placed on what can be done today.

At their core, medical cannabis discussions boil down to a lack of NHS prescribing and funding. Whilst this is incredibly frustrating for chronically ill patients and families of children that benefit from CBPMs, the NHS will only accept RCTs and sufficient health economic evidence to justify the high expenditure of such products.

Expanding the current prescribing framework to its maximum potential must be a priority. What does this look like? Essentially, increasing the number of clinicians currently prescribing cannabis to beyond the threshold that brings cannabis into the mainstream medical ecosystem.

The solution to expanding access within the scope of the current framework is grounded in clinical engagement. It is evident that the fear of the unknown can easily be overcome, with clinicians largely open to being objectively and appropriately educated on medical cannabis. Since a perception prevails of the unfamiliarity of medical cannabis and uncertainty regarding prescribing, any initiatives that provide clinicians with the confidence, understanding and skills to start prescribing are of tangible value.

The drive to expand private access to CBPMs will ultimately lead to an expansion of more widely and regularly prescribed medical cannabis in the private sector, with the potential for concrete health benefits to be observed by clinicians. This feedback loop can then influence researchers, mono specialist societies and other organisations to conduct further exploration into the opportunities and indications for cannabis prescribing.

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Declaration of Funding

Volteface is a London based advocacy and communications organisation, that seeks to reduce the harm drugs pose to individuals and society, through evidence-based policy reform. We cultivate fresh thinking and new ideas through our policy reports, online blog, audio-visual content and an ongoing events programme.

We work with an array of partners across advocacy, politics, business, media, academia and front line service provision to foster public engagement and formulate new evidence-based policy ideas. Whilst we are UK-based and focused, we pride ourselves on engaging with ideas and best practice from across the world.

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