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THEORETICAL AND METHODOLOGICAL PERSPECTIVE

Developing a real-world evidence base for prescribed cannabis in the United Kingdom: preliminary findings from Project Twenty21

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Abstract

The therapeutic potential of medical cannabis to treat a variety of conditions is becoming increasingly recognised. Globally, a large number of countries have now legalised cannabis for medical uses and a substantial number of patients are able to access their medications. Yet in the UK, where medical cannabis was legalised in November 2018, only a handful of NHS prescriptions have been written, meaning that most patients are unable to access the medicine. Reasons for this are manyfold and include the perceived lack of clinical evidence due to the challenges of studying medical cannabis through randomised controlled trials. In order to develop the current evidence base, the importance of incorporating real-world data (RWD) to assess the effectiveness and efficacy of medical cannabis has gradually become recognised. The current paper provides a detailed outline of Project Twenty21 (T21), the UK's first medical cannabis registry, launched in August 2020. We provide the rationale for T21 and describe the methodology before reporting the characteristics of the 'first patients' enrolled in the registry. We describe the health status of all patients enrolled into the project during its first 7 months of operation and the sociodemographic characteristics and primary presenting conditions for these patients, as well as details of the medical cannabis prescribed to these individuals. By 12th March 2021, 678 people had been enrolled into T21; the majority (64%) were male and their average age was 38.7 years (range = 18–80). The most commonly reported primary conditions were chronic pain (55.6%) and anxiety disorders (32.0%) and they reported high levels of multi-morbidity, including high rates of insomnia and depression. We also present preliminary evidence from 75 patients followed up after 3 months indicating that receipt of legal, prescribed cannabis was associated with a significant increase in self-reported health, assessed using the visual analogue scale of the EQ-5D-5L (Cohen's $d = .77$, 95% CI = .51–1.03). Our initial findings complement reports from other large-scale databases globally, indicating that the current RWD is building up a pattern of evidence. With many clinicians demanding better and faster evidence to inform their decisions around prescribing medical cannabis, the current and future results of T21 will expand the existing evidence base on the effectiveness of cannabis-based medical products (CBMPs).

Keywords Delta-9-tetrahydrocannabinol (THC) · Cannabidiol (CBD) · Cannabis-based medical products (CBMPs) · Real-world data (RWD) · Project Twenty21 (T21)

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Introduction

Cannabis as a medical treatment

Cannabis has been used in traditional medicine for millennia but was banned by most countries in the 1930s in a failed attempt to stop recreational use and after the League of Nations declared it had no medical value (Nutt 2019). Over the past three decades, interest and use had grown especially in the USA where the majority of states now allow medical cannabis which means the vast majority of the US population can access it. Cannabis is now a medicine in Canada and at least 20 other countries including the UK where it was made a medicine in 2018. However, in the subsequent 2 years, there have been very few prescriptions on the NHS despite estimates that over a million people self-medicate daily with illegally sourced cannabis (Couch 2020). Reasons for the very low prescribing on the NHS are complex and multifaceted. They include resistance from doctors and pharmacists plus the complex and time-consuming Department of Health regulations attached to products containing d9THC which is still a Class B Schedule 2 drug under the misuse of drugs act 1971 (Nutt et al. 2020). Project Twenty21, the topic of this paper, was set up to help address this problem.

Globally, there is increasing recognition of the therapeutic potential of cannabis-based medicinal products (CBMPs) for a broad variety of conditions and an ever increasing number of jurisdictions have now legalised these for medical use. In most countries, the provision of medical cannabis has evolved over time, often in response to patient demand and product developments (Schlag 2020).

Medical cannabis in the United Kingdom

In the UK, medical cannabis was legalised and made available under a Medicines and Healthcare products Regulatory Agency Specials Licence in November 2018 as a result of public controversy and campaigning (Nutt et al. 2020). Yet during the past couple of years, only a very small number of patients with a limited range of clinical indications have been able to access treatment with CBMPs within the NHS (Schlag et al. 2020). A slightly higher number of patients are able to access their CBMPs via private prescription, at considerable costs (Nutt et al. 2020). As such, access to regulated medical cannabis remains inaccessible for most patients in need. Many patients had to resort to the illicit market to purchase their product at considerable risk (Couch 2020; United Patients' Alliance (UPA) 2018).

Physicians are only slowly adapting to the new regulations and often feel uncomfortable in prescribing due to the ongoing controversy surrounding prescriptions, and the remaining stigma attached to 'cannabis'. Reasons for this resistance are discussed in detail in Nutt et al. (2020) and Schlag et al. (2020) offer suggestions of how to overcome these barriers to prescribing.

The current UK National Institute for Health and Care Excellence (NICE) guidelines recommend the prescription of only three cannabis-based medicinal products — Nabilone, Epidyolex and Sativex — for the treatment of four main conditions: chemotherapy-induced nausea and vomiting, spasticity of adults with multiple sclerosis (MS) and two rare but severe treatment-resistant epilepsies (National Institute for Heath and Care Excellence (NICE) 2019). In the UK, unlike in most other countries, medical cannabis can be prescribed for any condition. However, only specialists are allowed to initiate treatment and few potential prescribers feel comfortable to prescribe outside of NICE recommendations, for concerns over their insurance cover and the perceived lack of clinical evidence (Nutt et al. 2020).

The need for real-world data

In contrast to the limited recommendations in the current NICE guidelines, real-world data (RWD, also called real-world evidence or RWE) is increasingly highlighting that people are using medical cannabis for a broad variety of indications ranging from pain, depression, anxiety, insomnia, arthritis, fibromyalgia, muscle spasms, irritable bowel syndrome, Tourette's syndrome, migraines, headaches and more (e.g. BFarm 2020; Couch 2020; Haroutounian et al. 2016; Mahabir et al. 2020; Sexton et al. 2016; United Patients' Alliance (UPA) 2018).

As the rapid rise in the use of medical cannabis has not yet been accompanied by conclusive clinical evidence of its efficacy or effectiveness, there is a need for additional research to support the prescription and use of medical cannabis worldwide. Although randomised controlled trials (RCTs) are regarded as the gold standard of evidence, the unique properties of whole plant extract cannabis and the acceptance of its medicinal use in many countries worldwide present an opportunity for the use of RWD. RWD is an umbrella term for data regarding the effects of health interventions that are not collected in the context of highly controlled trials (FDA Framework for FDA's Real-World Evidence Program 2018). Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data (FDA Framework for FDA's Real-World Evidence Program 2018).

Globally, RWD for the effectiveness of CBMPs for a wide range of conditions has been increasing rapidly. Recent examples include the large-scale databases being developed by Health Canada (2015), BFarm (2020) in Germany and the Minnesota database (2020). For 2021, both the French and the UK governments have just announced that they would begin their own national databases to collect data on the effectiveness of CBMPs (Pascual 2020).

This paper provides a summary of Project Twenty21, the first UK registry for cannabis-based medical products. Specifically, we provide a rationale for the development of this project, describe the data collections methods to be used and also analyse results from patients enrolled into this registry during the first 7 months of its operation.

Methods

Launched in August 2020, Project Twenty21 (T21) is the first UK registry seeking to develop a body of RWD to inform on the effectiveness and safety of medical cannabis. T21 is a multi-centre, prospective, observational patient registry of RWD that aims to include data from patients receiving medical cannabis for a variety of conditions. Patients will be entered into the registry and followed for 2 years for data collection purposes at the same intervals used in standard of care.

Initially, the data collection includes patients prescribed cannabis for six indications, namely: (i) chronic pain, (ii) post-traumatic stress disorder (PTSD), (iii) anxiety, (iv) multiple sclerosis, (v) Tourette's syndrome and (vi) cannabis use disorder. We anticipate that the number of included indications will expand in the future. The over-arching goal of this project is to collect prospective data from substantial numbers of people who receive cannabis-based medicinal products (CBMPs) for a variety of conditions to contribute to both the scientific literature and regulatory aspects on the safety and effectiveness of these products in real-world settings. The study is designed to be prospective with clinical records accessed over the period for which patients remain in treatment.

Recruitment strategy and consent

UK regulations for receipt of prescribed cannabis stipulate that an individual must have an established diagnosis and evidence of failure of at least two treatment approaches before being eligible to legally receive prescribed CBMPs. Therefore, individuals receiving a prescription would have an established history of chronic — and treatment resistant — illness. Patients can self-refer to a prescribing physician at a clinic and are required to present all necessary documentation from their general practitioner, including:

- Evidence of diagnosis meeting one of the six clinical indications.
- Past medical history and comorbidities.
- Current medications.

Patients with evidence of one of the six indications are invited to participate in the registry. There were no inclusions of exclusion criteria specifically for participation in the registry: decisions about the suitability of CBMPs for a specific individual were entirely the responsibility of the treating physician. All individuals receiving a prescription will be invited to participate and, if they agree, consent will be obtained following Good Clinical Practice guidelines. As there is no clinical intervention as part of participation in the registry, patients consent only to the collection of their data. Patients under the age of 16 require proxy consent by a parent or guardian.

Prescribers partnering with T21 have access to a formulary that includes a range of cannabis-based medicinal products. There are a wide range of products available including oils and flower of differing CBD and THC ratios. However, there are no restrictions on what products can be prescribed and, indeed, they can prescribe products from outside the formulary, based on their own clinical judgement.

As part of their clinical assessment, in addition to providing information on their medical history, past and current treatments, patients are asked to complete a number of structured assessments of symptomatology, based on standardised and well-validated self-report questionnaires. Depending on clinician choice, these are either completed during the clinical appointment or prior to the appointment and reviewed by the prescriber as part of their clinical assessment.

Measures

All patients complete a health-related quality of life questionnaire, a questionnaire to assess their perception of their treatment, questions regarding sleep and insomnia and mood. The outcome measures completed at the patient's first visit to the clinic and at subsequent visits that the patient attends, as per standard of care at the clinics. In addition, patients are asked to complete questions specific to their primary condition.

Measures assessed for all patients include the following.

Health-related quality of life The health-related quality of life instrument that will be used in this registry is the EuroQol 5 Dimensions (EQ-5D). It is a widely used, validated

and reliable tool that assesses the quality of life of patients in many disease areas (Devlin et al. 2018) through assessment of the severity of each of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

Mood/depression The outcome measure that will be used for depression is the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a reliable and valid measure of depression severity and is composed of a 9-item self-rated instrument that has been validated in general populations, medical populations and psychiatric samples (Rancans et al. 2018). Registry patients with chronic pain, PTSD, anxiety and substance use disorder will complete this questionnaire at their first visit to the clinic and at subsequent follow-up visits.

Sleep All patients enrolled into T21 were assessed using four items querying their usual duration and intensity of sleep as well as daytime sleepiness. These items were adapted from the widely used Pittsburgh Sleep Quality Index (Buysee et al 1989). Each of these items was assessed on a five-point scale: How much sleep patterns were interfering with daily activities (not at all, a little, somewhat, much, very much). Difficulties falling asleep, difficulties staying asleep and waking up too early were each assessed using the scale: none, mild moderate, severe, very severe.

Condition-specific measures of illness severity

In addition, individuals with specific primary conditions complete the following assessments.

Chronic pain The primary outcome measure for patients with chronic pain is the Brief Pain Inventory Short Form (BPI-SF). The BPI-SF is validated for use in patients with both cancer and non-cancer pain (Keller et al. 2004) and is one of the most commonly used measurement tools for evaluating clinical pain, including pain severity and the interference of pain on feeling and function (Cleeland 1991).

PTSD The primary outcome measure for patients with PTSD is the Posttraumatic Stress Disorder Checklist-Civilian Version (PCL-C). The PCL-C is a reliable and validated tool to provide assessment on PTSD symptom change and is a widely used self-report measure to assess the symptoms of PTSD, as well as being a tool for the provisional PTSD diagnosis (Conybeare et al. 2012).

Anxiety The primary outcome measure for patients with anxiety is the Generalised Anxiety Disorder 7-Item Scale (GAD-7). The GAD-7 is one of the most frequently used, validated, self-reported questionnaires that is used to screen for, diagnose and assess the severity of generalised anxiety disorder (Jordan et al. 2017).

Multiple sclerosis The primary outcome measure for patients with pain from multiple sclerosis is the BPI-SF. In addition to this, the Expanded Disability Status Scale (EDSS) will also be used. The EDSS is an internationally accepted, widely used tool to measure the disease progression in multiple sclerosis that has been evaluated for its validity and reliability (Meyer-Moock et al. 2014).

Tourette's syndrome The primary outcome measure for patients with Tourette's syndrome is the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a reliable tool for measuring tic severity in Tourette's syndrome and is reported to be internally consistent for its measures across adults and children (Storch et al 2005).

Cannabis use disorders The primary outcome measure for patients with substance use disorder is the Severity of Dependence Scale (SDS). The SDS is a short, 5-item scale for measuring the degree of dependence experienced by users (Gossop et al 1995) and its score is related to behavioural patterns of drug use, which indicates substance dependence. The psychometric properties of the SDS are very reliable across different populations.

Additional data to be available at 3-month and subsequent follow-ups

Patient follow-up will adhere to standard of care at each clinic and will not differ based on inclusion in the registry. Follow-up is typically completed every 3 months (13 weeks) and patients will complete all standard follow-up questions, including questions pertaining to insomnia and health-outcome questionnaires at any visits they attend. Patients withdrawing from treatment will be identified and any additional visits will be recorded as an unscheduled visit. Additional data that will be available include the following.

Perceived adequacy of treatment

Patients will be asked as part of their follow-up visits whether they believe that their prescribed medical cannabis has been adequate in treating their respective condition. Patients will also complete the Patients' Global Impression of Change (PGIC) scale, regarded as an important indicator of the impact of treatments (Scott and McCracken 2015), at each follow-up visit.

Adverse effects

Data on any side effects, including any serious adverse events, reported during follow-up assessments with their prescribers will also be available.

The current analyses focus on data collected during the initial baseline assessment, conducted before individuals receive a prescription for cannabis. Therefore, these data are not reported in the current analyses.

Final patient status

Patients will remain in the registry for 2 years. For patients who cease attendance at a clinic for their medical cannabis prescription, all data entered prior will remain in the database. If a patient chooses not to have a prescription renewed, the reason will be recorded, if possible.

Ethics

According to the National Health Service Health Research Authority, Project Twenty21 is classified as research; however, based on the Medical Research Council decision tools, Research Ethics Committee review and approval is not required. All individuals did, however, provide signed informed consent for their data to be used for research purposes.

Current methodology and statistical analyses

In addition to the detailed outline of T21 above, the current paper provides a description of the health status of all the patients enrolled into the project during its first 4 months of operation, from 1st August 2020, to 12th March 2021. Specifically, this paper will:

a) Describe the sociodemographic characteristics and primary presenting conditions for these patients.
b) Detail their health status.
c) Describe the range and characteristics of cannabis-based medicines prescribed to these individuals.
d) Present an initial analysis comparing self-reported health status, assessed using the visual analogue scale of the EQ-5D-5L, at baseline and 3 months in the first patients to complete a 3-month assessment ($n = 75$).

Descriptive statistics (means, proportions) were generated in SPSS and, as the aims of these analyses were purely descriptive, no inferential statistics were conducted. In addition, we report the results of factor analytic and reliability analyses conducted to establish the reliability of specific health assessments within this population.

Results

Sample characteristics and primary medical condition

As of 12th March 2021, a total of 678 individuals had been identified as seeking treatment from a clinic affiliated with T21. The majority of this patient group were male (64.0%) and their average age was 38.7 years (range = 18 to 80). There were 13 separate prescribing clinics contributing data with some of these clinics including multiple prescribers. Prescribing Doctors were from a variety of specialties including Psychiatry, Neurology, Anesthesiology and Pain.

Figure 1 summarises the primary condition for these individuals who received prescribed cannabis: the majority (55.6%) were being treated for chronic pain while 32% were being treated for anxiety disorders, 6.7% for PTSD, 3.3% for multiple sclerosis and less than 1% were being treated for each of cannabis use disorders, epilepsy and Tourette's syndrome.

In addition, 87% of the sample reported at least one additional comorbid or secondary condition with many individuals reporting a substantial number of comorbid conditions: 29.4% of the sample reported one or two comorbid conditions, 33.0% reported three to five and 24.6% reported six or more secondary conditions. The most commonly reported secondary conditions across the entire sample were depression (43.1% of the sample), back and neck problems (32.3%), insomnia (30.5%), stress (30.4%), anxiety (28.5%) and neuropathic pain (20.4%).

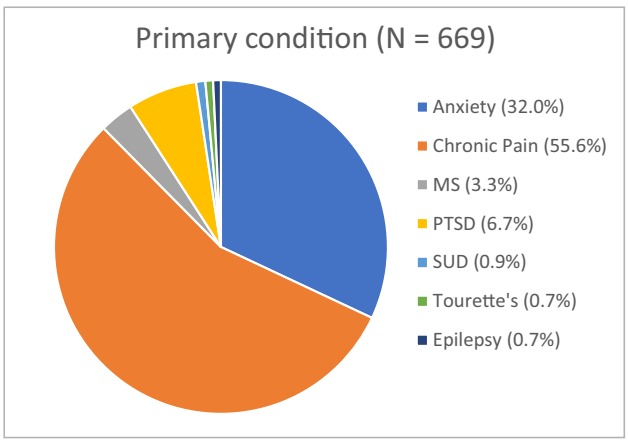

Fig. 1 Primary condition ($N = 669$)

Table 1 Distribution of PHQ depression items and depression classifications ($n=609$)

PHQ-9 scores	Depressive classification	% of sample
0–4	None/minimal	9.7%
5–9	Mild	18.1%
10–14	Moderate	21.6%
15–19	Moderately severe	23.8%
20–27	Severe	26.8%

Prior experience with cannabis

A total of 14.9% of the sample reported that they had not previously used cannabis while nearly two-thirds of the sample reported that they were currently using cannabis (63.0%) and that the primary reason for using cannabis was to treat their index condition (63.4%). Among the 152 individuals currently using cannabis to treat their index condition, 54.1% reported that they were using it daily.

Depression

Depression was assessed using the PHQ-9 questionnaire (Rancans et al 2018), a nine-item scale which assesses the frequency of depressive symptomatology during the preceding 2 weeks on a four-point scale (0 = not at all; 1 = several days; 2 = over half the days; 3 = nearly every day). These items can be summed to form an overall measure of depressive symptomatology.

In the current sample, this measure had excellent reliability, as assessed using Cronbach's alpha ($\alpha=0.89$), and a summary of the distribution of this scale, along with suggested diagnostic labels, is provided in Table 1: It can be seen that approximately half the sample reported moderately severe (23.8%) or severe (26.8%) depression; only 9.7% of the sample reported no or minimal symptoms of depression.

Quality of life

The EQ-5D-5L contains five items, each assessed on a five-point scale, and responses to these questions in the current sample are summarised in Table 2. It can be seen that across the five dimensions, the number of people reporting no problems ranged from 12.2 (for anxiety/depression) to 45.0% (for self-care) while, at the other extreme, the number of people reporting that they had severe problems or were unable to function ranged from 9.3 (for self-care) to 36.6% (for usual activities).

By convention, it is also possible to convert ratings on each of the five health categories to a single score, using consensus judgements of the relative desirability of each of these disease states. Using the English population value set described by Devlin et al. (2018), it was possible to construct this index score for the current sample and compare it with population-based norms for England. Several features of these data are noteworthy: firstly, the maximum score (1.00) representing no problems in any of the five dimensions was reported by only three participants in this survey, compared with 47.6% of those in the normative population sample. Secondly, health status of zero or less, corresponding to a health status judged to be equivalent to or worse than being dead by the English general population, was reported by 5.4% of those receiving cannabis.

The EQ-5D-5L also contains a visual analogue scale where individuals are asked to rate their health today on a 100-point scale where 0 means the worse health they can imagine while 100 means the best health they can imagine. Means score on this scale, across the entire sample, was 47.3, which is considerably lower than the previously estimated normative value for the United Kingdom population (85.7; Jansen et al. 2018).

Sleep

Although sleep was not one of the primary qualifying conditions for T21, it forms a key transdiagnostic component of many of the disorders being studied including anxiety/depression and pain. Additionally, and consistent with our own findings, it is a commonly reported problem among individuals prescribed cannabis-based products. For that reason, all patients enrolled into T21 were assessed using four items assessing the duration and intensity of sleep as well as daytime sleepiness. Each of these items utilised five-point

Table 2 Mean scores on EQ-5D-5L dimensions ($n=654$)

Extent of problems	Mobility	Self-care	Usual activities	Main	Anxiety/depression
None	36.4	45.0	12.8	12.4	12.2
Slight	19.4	21.9	15.7	18.2	23.5
Moderate	24.9	23.9	34.9	33.5	30.6
Severe	17.1	7.2	28.6	27.7	19.6
Unable to walk/wash/usual activities/extreme	2.1	2.1	8.0	8.3	14.1

response categories and assessed: How much sleep patterns were interfering with daily activities (not at all, a little, somewhat, much, very much) while three items assessing difficulties falling asleep, difficulties staying asleep and waking up too early were each assessed using the scale: none, mild moderate, severe, very severe.

Reports of sleep quality were available for 640 individuals. Consistent with the previous results, analysis of these data indicated that many of this patient group experienced substantial difficulties with sleep: 52.7% reported that their sleep patterns interfered with their daily activities much or very much, while 41.6% reported severe/very severe problems falling asleep, 40.5% experienced severe/very severe problems staying asleep and 34.5% reported severe/very severe problems waking up too early.

Product characteristics

As of 12th March 2021, the T21 formulary included a range of products varying in the route of administration and concentrations of THC and CBD. However, consistent with the observational nature of T21, prescribers who contributed to the project were not limited in the products they could prescribe and were able to prescribe non-T21 products. Given the expectation both that the number and range of products available through T21 will expand and that many doctors will prescribe products from outside this formulary, we will not be analysing the data using product-specific indicators of use but will, instead, be coding product information to provide measures of: (a) route of administration; (b) THC concentrations and (c) CBD concentrations. Table 3 provides a summary of the preparation type (oil vs flower) and relative THC and CBD potencies for the products prescribed up to this date. It is notable that, while the majority of products prescribed were oils (59.9%), there was considerable variation in the potency of both CBD and THC and in the relative balance between these two components.

Quality of life at 3-month follow-up

By 13th March 2021, a total of 75 individuals had completed both baseline and 3-month follow-up. Of these, 64.0% were male, 34.7% female and one individual identified as non-binary. Their average age was 39.9 years (range = 20.2–75.7); 56.0% reported a primary medical condition of chronic pain, 32.0% anxiety, 6.7% multiple sclerosis and 5.3% PTSD. The mean delay between these patients' first appointment and follow-up was 88.1 days (range = 48–133, SD = 19.8).

Table 3 Characteristics of prescribed products

	Oil	Flower
High CBD	12.1%	1.5%
Balanced	38.9%	4.6%
High THC	4.4%	38.5%

Current health was assessed at both time points using the visual analogue scale of the EQ-5D-5L. At baseline, the mean rating on this scale was 40.7 (SD = 19.7). At 3-month follow-up, when this assessment was repeated, the mean self-reported health score was 61.5 (SD = 18.8). The mean difference (20.9, 95% CI = 14.6–27.1) was statistically significant ($t = 6.7$, $df = 74$, $p < 0.0001$). The effect size estimator (Cohen's d) was 0.77 (95% CI = 0.51 to 1.03), indicating a large effect of prescribed cannabinoids on improved health.

Discussion

In this paper, we have described the individual characteristics and health status of patients seeking treatment with medicinal cannabis through doctors affiliated with T21. By 12th March 2021, 678 individuals had presented with a range of primary conditions but with the most prevalent primary conditions being chronic pain and anxiety. These findings echo outcomes of other registries globally (e.g. Health Canada, BFarm, Minnesota), indicating the development of a pattern of evidence through RWD. In light of the relative lack of RCTs for many of these conditions, RWD, such as T21, can complement the still developing clinical data and, as such, play a significant role in the evaluation of the effectiveness and efficacy of CBMPs.

Perhaps the most striking feature of this sample was their relatively poor health: in addition to their primary condition, all patients reported at least one secondary condition with 36.2% reporting five or more co-occurring conditions, in line with Mahabir et al. (2020) findings. This impression was also confirmed by responses to standardised questionnaires which indicated that the sample had high levels of anxiety/depression, pain and also experienced considerable difficulties with sleep. Perhaps the most striking demonstration of the poor health of this group came from analyses of the EQ-5D-5 l, given that there are England-wide norms for responses to this widely used and well-validated questionnaire.

Together, these results indicate that the patients receiving medically prescribed cannabis were, in general, experiencing moderate to severe health problems and had a quality of life substantially lower than the general population. The relatively poor health status and high level of comorbidity has been previously highlighted (e.g. Mahabir et al. 2020; Salazar et al. 2019). In the Minnesota database, 67.2% of currently enrolled patients are certified for more than one condition.

While of major importance to patients (Schlienz et al 2020), quality of life has not been addressed in detail in

other large-scale databases, highlighting the importance of including these measurements in T21 to develop the current evidence base.

Although there is the demand for more RCT evidence, our preliminary analyses also highlight both the advantages and challenges of analysing real-world data. Firstly, patient accrual has occurred relatively rapidly and the study is likely to achieve sample size many times higher than that of typical trials. This is partly achieved by allowing greater heterogeneity in the registry, both in terms of patient characteristics, primary and comorbid conditions and the range of treatment (products) being prescribed. This will lead to complexity in the analyses and, for many analyses, reduced statistical power. Nonetheless, the considerable comorbidity we have documented in this sample highlights a major limitation of randomised controlled trials. These studies typically restrict participation to a relatively narrow patient population characterised by: a single (target) condition with no comorbid conditions while age and other exclusion criteria may also be applied. Our own analyses have demonstrated that multiple comorbid conditions are, in fact, the norm and suggest that a sample consisting of only those with comorbid illness would be unrepresentative of the patient group. This and other limitations of RCTs may potentially help explain the numerous instances across medicine in which a treatment which has been shown to be efficacious in trials may not be effective in real-world settings. What we need now is outcome data for the diagnoses and symptoms included in Twenty21. This will be forthcoming over the next year or so.

One challenge of RWD, where the researcher has no control over data collection but is instead reliant on data collected for other (clinical or administrative) purposes, is that there is often a larger degree of missing data than is typical in more tightly controlled (and more costly) trials. This was evidenced by the amounts of missing data in the current report (as highlighted in the tables). Coding RWD, particularly data such as prescriptions when products from outside the formulary could be prescribed, can also be time-consuming. Missing data results in a loss of statistical power but, under the assumption that data are Missing Completely at Random (MCAR), will not affect the validity of our conclusions. In subsequent analyses, we will be able to test for any potential biases in patterns of missingness and potentially correct for these using techniques such as data imputation.

Future research in T21

Despite the limitations of RWD, when combined, various global databases, including T21, show an emerging pattern of evidence which ought to be taken account when regulating the prescription of CBMPs. With many clinicians demanding better and faster evidence to inform their decisions around prescribing CBPMs, findings from RWD may offer potential solutions to the lack of RCTs. Future research in T21 will focus on examining the effectiveness of cannabis-based medical products in reducing symptomatology across different primary conditions and on improving quality of life. We will also examine the extent to which use of these products may alter use of other prescribed pharmaceuticals (e.g. opioids). Capitalising on the strengths of real-world data (e.g. large sample size and heterogenous patient characteristics), we will also examine whether the longitudinal trajectories of symptomatology and quality of life may vary between patient groups (e.g. those with specific patterns of comorbidity or co-occurring treatment). Finally, the availability of longitudinal data on patterns of use will allow an examination of the potential development of tolerance while we will also collect information on any side effects or adverse reactions. Together, this information will provide a solid foundation to assess the safety and effectiveness of prescribed cannabis in the 'real world' and the extent to which safety and effectiveness may vary between product types or patient characteristics.

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Declarations

Conflict of interest CS was clinical director of T21 until September 2020. AKS is head of research at the charity Drug Science. ML is head of data at Drug Science. DJN is chair of Drug Science.

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