

# RCPsych Review of Cannabis: medicinal cannabis and cannabis for recreational use



## Call for Evidence

---

### About the Review

The Royal College of Psychiatrists is undertaking a review to develop a College position on:

- cannabis use in the UK and how this relates to mental health, incorporating evidence on the biological, psychological and social effects of cannabis
- the use of medicinal cannabis in relation to mental illness.

### About this Call for Evidence

RCPsych's review is beginning its work by asking those with expertise and personal experience of medicinal cannabis and cannabis for recreational use to provide relevant evidence. Those who might wish to respond are:

- Academics with experience in these fields;
- patients/service users;
- carers and family members;
- members of staff in mental health services (NHS, independent, or voluntary);
- providers of mental health services (NHS, independent, or voluntary);
- charities or voluntary sector organisations with an interest in this area;
- individuals or organisations working in the criminal justice system;
- other relevant people, bodies or groups.

Responses will be used to inform our areas of inquiry and final reports.

### Please read carefully

In completing this consultation, you should understand that your responses may be quoted and used in reports or other outputs from the College.

If you would like us to anonymise your response (i.e. so that you or your organisation cannot be identified in any reports or outputs), then please tick or mark this box:

### What this consultation covers

RCPsych's review and this call for evidence cover two separate areas – recreational use of cannabis and medicinal cannabis.

The RCPsych's review extends UK-wide, which will be the context in which it writes, though we are looking to collect all the relevant evidence internationally.

### Recreational cannabis

This consultation is looking to gather evidence on recreational cannabis use and will focus on the following topics:

- The prevalence and strength of cannabis used in the UK;
- what effects cannabis use has directly on the likelihood of people developing mental illness;

- criminalisation and marginalisation of cannabis users in the UK and the effects this has on people's mental health;
- synthetic cannabis;
- why people start to smoke cannabis, where this leads them and why they continue or why they stop;
- effects of changes in services in the UK;
- global evidence of effects of different legal approaches;
- reducing mental health harms of cannabis use;
- priorities for research.

### Medicinal cannabis

This consultation is looking to gather evidence on medicinal cannabis and will focus on the following topics:

- Medicinal cannabis used to treat mental illness;
- Guidance for clinicians prescribing medicinal cannabis;
- Research needed on medicinal cannabis used to treat mental illness and the barriers to this research;
- Any links between the prescription of medicinal cannabis and the prevalence of recreational use;
- pathways in and out of cannabis for medicinal use.

### How to respond to this consultation

This consultation is looking to gain a clear perspective on what the evidence base is on both areas – we ask that people focus on firm evidence, and limit stating personal opinions as much as possible. Please do not feel you have to answer all the questions below – please limit your responses to what you consider to be your area of expertise and where you feel you can add value.

Please provide references wherever possible.

The below boxes are not sized to anticipate answers, please expand as required, do keep your answers as brief and as pertinent as possible.

**Please return a completed version of this form to [policy@rcpsych.ac.uk](mailto:policy@rcpsych.ac.uk) by 5pm on Monday 10<sup>th</sup> June 2019.**

### **About you**

Name:	
Organisation name (if responding on behalf of an organisation).	DrugScience

### **Part1: Recreational Cannabis**

## Part 1A: Prevalence of cannabis in the UK

1. What is the prevalence of recreational cannabis use in the UK? How has this changed over the past ten years?

Comprehensive data on the prevalence and extent of cannabis use among the UK general population are lacking. The best source may be results from the annual Crime Survey of England and Wales which suggests that, while cannabis is the most commonly used illicit drug, rates of use have declined over the past 20 years (Crime Survey for England and Wales, 2018). Rates of past year use are higher among those aged 16-24 but have declined from ~25% (in 1996) to ~16% (in 2017/8) of the English/Welsh population. The same yearly figures for 16-59 year olds also shows a decline (~10% to ~7.2%).

2. What evidence is there for the strength of cannabis used in the UK? How has this changed over the past ten years?

There is limited data on the potency of cannabis products on the illegal market: nonetheless, the available evidence indicates that, while the potency of cannabis products has remained largely unchanged over the past decade, high potency strains (sinsemilla), with THC potency in the region of 14-15%, have come to dominate the market. The THC potency of street cannabis has increased markedly over the past two decades alongside a reduction in CBD levels (El Sohly et al, 2014; EMCDDA, 2018; di Forti et al, 2019) and this is associated with a parallel increase in numbers of young people entering treatment for cannabis dependency (EMCDDA, 2018; Freeman et al, 2018). Although the rise in THC potency was seen first with herbal forms (e.g. skunk) recently there has been a similar increase to ~15% in resin/hash forms (EMCDDA, 2019).

3. What is the evidence on the regional differences of the prevalence and strength of cannabis in the UK?

High potency strains with THC potency in the region of 14-15% or more have come to dominate the market and, within the London and surrounding market, may comprise in excess of 90% of all cannabis available. This increase appears to mirror trends throughout Europe for increasing THC potency. These high potency varieties generally have very low, if any, cannabidiol (CBD). However, these other forms are still available and used in the UK. Using data from over 3000 last year cannabis users from England, recruited to the Global Drug Survey (GDS, 2019), the most commonly used type was high potency herbal preparations among 55%, normal weed among 34%, resin 7.4% and concentrates among 1.1%. Of interest 13.7% had reported use of concentrates in the last year, with their use likely to be associated with higher rates of dependence and poorer mental health (Chan et al, 2017). The types of cannabis available also impacts on how people use, with concentrates supporting vaping. Most people in the UK (75%) usually mix with tobacco and this is an area of public health focus that has been overlooked. Any drug policy should encourage people away from tobacco routes of administration (Hindocha et al, 2016). GDS 2019 shows that 38% reported the use of any edible form of cannabis in the last 12 months.

4. What evidence is there for presence of contaminants such as fentanyl in cannabis used in the UK? How has this changed over the past ten years? Are these trends replicated globally? Have different legal approaches around the world had an effect on these trends?

We know of no evidence for this.

## Part 1B: The link between cannabis and mental illness

1. What evidence is there for a link between cannabis use and mental illness (psychosis and others)? What is the strength of the evidence? *When answering this question, please consider which individual components of cannabis are relevant and how other factors such as age, frequency of use, genetics etc. affect the levels of risk involved and specify the extent to which evidence points to causation or association.*

The major concern – and greatest research attention – has focussed on whether cannabis use may increase risks for the development of SMI/ psychosis. In addition there have been concerns that cannabis use, and particularly use during adolescence, may increase risks for major depression and suicidal behaviours (Gobbit et al, 2019).

The strongest predictors of whether any given individual would have a psychotic disorder or not are self-reported daily use of cannabis and use of 'high-potency' cannabis as defined by the term used to describe their type of cannabis (e.g. 'skunk' versus 'hash/resin') (Di Forti et al, 2019). No biological measures of cannabinoids were used in this study but the higher potency varieties like skunk generally refer to increased THC and low - if any - level of CBD. Low potency varieties did not increase rates of psychosis. The association between cannabis use and psychosis is influenced by several vulnerability factors, including genetics (Morgan et al 2016; Di Forti et al, 2012) and environmental factors (Gage et al, 2016) as well as the frequency and type of cannabis used (Di Forti et al, 2019). Evidence linking cannabis use with the development of depression and anxiety is less consistent, although these disorders are often comorbid with cannabis addiction. Age of onset is also a key risk factor, with first use before the age of 16 being associated with the greatest risk. Family history of psychosis also predicts risk (McGuire et al, 1994).

Yet despite suggestions in the cannabis/ psychosis literature that the potential harms of cannabis may be reduced if products high in CBD are used, none of the literature on cannabis use and *depression* has yet explored potential differences by type/ potency of cannabis. This has become a difficult area of research as street cannabis with appreciable levels of CBD are now rare. There are also methodological problems in many studies with pre-existing differences between 'users' and non-users, the measure of exposure (cannabis use) in some studies is also questionable. For example, in their meta-analysis, Gobbit et al (2019) include an early study (Fergusson et al, 1996) that compared individuals who had ever vs never used cannabis. Given the low frequency of use among ever users in this (young) cohort, it can be argued that any association between cannabis use and outcomes is unlikely due to pharmacological effects but may reflect: a) uncontrolled confounding; b) social effects of cannabis use (e.g. if a young person gets into trouble with parents/ school/ police for possessing cannabis that could be a risk factor for depression).

The acute effects of cannabis on cognitive function are well documented, and the most robust, dose-related decrements are to working and episodic memory. Its long-term cognitive effects remain controversial, are influenced by many confounds and appear to subside within days after stopping use of the drug (Curran et al, 2016). Again age of use appears to be important with the Dunedin longitudinal study (Fergusson et al, 2014) indicating it was only use before the age of 18 years that predicted any long term cognitive deficit.

The eCB system plays a major role in neurodevelopmental and maturational processes including synaptic pruning and white-matter development, and these processes are especially prevalent during adolescence. As exogenous cannabinoids affect the functioning of the eCB system, it is plausible that prolonged use during adolescence disrupts the neurodevelopmental maturational processes during this period. Thus, the human brain may be more vulnerable to drugs at the time when use of cannabis often begins. There is now evidence in humans that adolescents differ significantly from adults in their response to acute cannabis (Mokrysz et al, 2016).

## Part 1C: Criminalisation of cannabis

1. What evidence is there on the extent to which laws criminalising cannabis-based activities are being enforced?

Data from over 3000 people living in the UK who reported using cannabis in the last year who took part in GDS2014 can shed some light on how the laws have been implemented. 15.7% (n=468) reported been found in possession of cannabis by the police in the last year, with >80% reporting the amount was 1gm or less. Of the 468 people who were found in possession, a third were let off (no formal action), just over 20% received a cannabis warning or a penalty notice (on spot fine) and a similar proportion a caution. About 10% ended up in court. This section of questions will be repeated in GDS2021.

According to Government statistics, between Jan18-Dec18, there were some 86,103 persons in E&W convicted of possession of cannabis. It is conceivable that a number of those persons would have been (at the moment of arrest or charge) prosecuted for that and other offences. Some 5090 persons received a Penalty Notice for Disorder (i.e. aged 16+ in the 12 months ending Sept 2018). There were 27,017 cannabis/khat warnings ending Sept 2018 (only a minority would relate to khat). Regrettably, Offences involving the production and distribution of cannabis are subsumed within the general category of "Trafficking in controlled drugs" for the purposes of the Government recorded crime statistics.

2. What are the reasons for law enforcement's attitudes to the criminalisation of cannabis?

Talking to police it appears most Local Area Commands are reluctant to introduce defined possession amount levels or have strict guidelines on how to manage this. Front line police often it is the attitude of the person that determines what happens to them. Be nice and polite is much better than being rude and offensive.

This question is unhappily framed. Criminalisation has been a matter of UK *government* policy albeit (arguably) influenced by international drug policy. The question presumes that law-enforcement agencies (i.e. investigating agencies) have an "attitude" towards criminalization. It is not clear whether the question assumes that the Crown Prosecution Service is encompassed within the expression "law-enforcement". It is doubtful that the CPS would regard itself as a law-enforcement agency. Prior to January 2006, when powers of arrest, by a police officer, were extended to any offence (rather than in respect of "arrestable offences" carrying a sentence of 5 years or more), the police resisted the reclassification of cannabis from Class B (5 years max for possession) to Class C (2 years max for simple possession). One reason was the loss of the power of arrest. This issue fell away after January 2006. Anecdotal reports vary as to police policy regarding the intensity of enforcement in respect of the possession of cannabis.

3. What evidence is there for the different ways people are affected following criminalisation?

The criminalization of cannabis users can have greater detrimental effects on their lives than any harms related to their cannabis use. Ethnic minority groups are more prone to criminalization than white users. Data from GDS2014 found that the impact of getting caught in possession of cannabis was varied, with 12% reporting it had an impact upon employment, 14.1% had impact upon travel and 7.3% had an impact upon study.

### Part 1D: Marginalisation of cannabis users

1. What evidence is there of other forms of marginalisation caused by use of cannabis – exclusion from school, losing jobs, stigma etc.?

Please see above. GDS2017 has data on cannabis and stigma but this has not yet been analysed.

The stigma of recreational cannabis use has tainted medical uses. Because of the reluctance of physicians to prescribe medical cannabis, large numbers of people are using cannabis acquired through the black market, with all the risks this entails. People who are using cannabis for medical purposes to treat symptoms of serious illnesses are marginalised as they are being treated as criminals.

Further, users seeking treatment are also marginalised as medical services have a clear focus on alcohol and opioid users. This has marginalized the cannabis using population who have health needs and pushed them away from mainstream health services. This is particularly evidence in drug and alcohol services due to a prioritization of focus secondary to widespread funding cuts to services in England. Due to this prioritization there is an under-representation of service users from BME backgrounds who are more likely to use cannabis or crack cocaine rather than opioids or alcohol.

2. How many people are affected by this and in what way are they affected?

It is difficult to estimate exact numbers of affected people. Since marginalisation can take many different forms (and cannabis is widely used), numbers are likely to be high.

## Part 1E: Synthetic cannabinoids

1. What effect have synthetic cannabinoids had on the use of cannabis in the UK and mental health in general and what effects has it had on the groups in which it is used most commonly?

Synthetic cannabinoids (SCs) have become increasingly popular in recent years as their chemical structure is not detected by conventional cannabis urine drug screens. They are generally much more potent than herbal cannabis as they are full agonists at the CB1 receptor whereas cannabis is a partial agonist. SCs are also inexpensive. The explosion of their use has been seen in UK prisons and among marginalized populations such as the homeless (Akram et al, 2019). Because synthetic cannabinoids do not contain terpenes they do not have the characteristic smell of herbal cannabis. This makes surreptitious use easier which in turn encourages use in people with mental illness, especially those in hospitals.

Diverse in chemical structure, many have been subjected to legislative regulation, but their availability and use persists. Often marketed to reflect their similar effects to cannabis, their use has been associated with a range of negative health effects. They potentially pose a greater risk to users' health than natural forms of cannabis. Most people however given the choice will choose natural cannabis over SCs (Winstock and Barrat, 2014), with natural cannabis giving more positive and less unwanted effects. The relative risk associated with the use of SCs is significantly higher than that associated with cannabis. When seeking emergency hospital treatment significantly more symptoms were reported by respondents seeking treatment for SCs than for cannabis (Winstock et al, 2015), with the acute risk of seeking emergency medical treatment being increased by 30 times. Withdrawal tends to be more intense and physical in nature and occurs at lower levels of use than natural cannabis (Winstock et al, in preparation). Rates of dependence are also much higher than natural cannabis (Winstock et al, under review)

Regulation is unlikely to remove SCs from the market, so well-informed user-focused health promotion messages need to be crafted to discourage their use (Winstock, 2015).

## Part 1F: Pathways in and out of cannabis

1. What evidence is there for why people start to use cannabis for recreational use, where this leads them and why they continue or stop?

Initiation of cannabis use, which almost exclusively occurs during adolescence, is largely due to various social factors: initiation is via friends/ peer group and, as with tobacco or alcohol, is driven by curiosity and novelty seeking. Self-reported initial reactions to cannabis are largely positive but only a minority of those who have ever tried cannabis go on to use it more than a handful of times (Fergusson et al, 2003).

Escalation to frequent (e.g. daily) or dependent use may be more common among 'at risk' youth and, in particular, those who also use tobacco, alcohol and other drugs heavily (Hines et al, 2016). Earlier onset may also be marker of other problems / disadvantage. Based on data from over 5000 cannabis users from GDS2018 the major motivations for quitting are effects on motivation, mood, education, relationships with partner/family. Impacts on work and physical health were also cited as very important/important by 45%. Legal issues were the least significant factor. Most (>90%) quit without involvement from any health / treatment groups.

### Part 1G: Services:

1. What evidence is there for changes in services in the past 10 years affecting the use of cannabis in the UK and the harms associated with it? *Please include details of all relevant services, including addiction, mental health, children's and social services.*

Over the past 10 years there has been a substantial reduction in the provision of addiction services in the UK: in 2008 24053 young people (<18 years) entered addiction treatment services but this has declined to 15,583 in 2017-18, a 35% reduction (PHE, 2018). This reduction appears not to have been driven by a reduction in the numbers of youth experiencing problems with alcohol and other drugs. Nonetheless, in parallel with the reduction in overall number of youth receiving treatment there has been a marked increase in the percentage of young people receiving addiction treatment who present with a primary drug problem related to cannabis: This has increased from 53% in 2008-2009 to 77% in 2017/18. In addition, a further 11% of youth in addiction treatment were described as having a secondary problem with cannabis.

2. What evidence is there of outcomes of patients treated for cannabis-related disorder in mental health services?

Due to a reduction in funding for drug and alcohol services in the UK there has been a narrowing of priorities for drug and alcohol services. Services are now focused on opioid and alcohol users and thus there is very little direct treatment for people with cannabis-related disorders. People with cannabis-related disorders will be treated on an ad-hoc basis usually if there are other significant risk issues or vulnerability factors. There is often pressure from general adult mental health services for help with treatments for cannabis dependence in patients with co-existing psychotic disorders, most often in early intervention services which is a younger patient group more likely to use cannabis. Drug and alcohol services may support these core mental health services with offers of motivational interviewing or in exceptional cases a cannabis 'detox' using chlordiazepoxide, most often in the community but very occasionally as an inpatient. As this is done on an add-hoc basis and is rare compared with the level of need or demand there is no reliable evidence of outcome data for these kind of interventions.

As there are no effective pharmacological treatments for cannabis use disorder, existing treatments are psychological (e.g. CBT, motivational enhancement, contingency management). Abstinence rates at the end of treatment are around 10-30% (Budney et al, 2007) although some individuals reduce their extent of drug use rather than aim for abstinence. This figure of 30% abstinent at 6 months is similar to that reported by people in GDS2018.

## Part 1H: Global Evidence of effects of different legal approaches

1. What is the global evidence of the effects that different legal approaches to use, supply and production of cannabis have on use of cannabis (including prevalence of use, purity, components and strength) and the effects on mental illness and rates of mental illness?

Particularly in North America there have been recent changes in laws surrounding the possession and supply of cannabis products with a number of US States adopting a model for the provision of cannabis modelled on that for alcohol. In contrast to this highly commercialised model, Canada and Uruguay have adopted less commercialised approaches to legalising cannabis. These changes are relatively recent and it may be too soon to evaluate the public health impact of these changes. Changes that have occurred: 1. dramatic reduction, but not elimination of an illegal market; 2. proliferation of cannabis products (e.g., edibles, vaping) that may include safer routes of administration and 3. a steep reduction in the price of cannabis.

Despite these changes within cannabis markets in some US States, there is little evidence that rates of use have increased, although this remains contentious and it is probably too soon to adequately assess the health effects of these legal changes (Hall and Lynsky, 2016).

## Part 1I: Reducing harm

1. What evidence is there on the most effective methods of reducing the mental health harms associated with cannabis use and the specific effects of cannabinoids?

There is accumulating evidence that, among those who are vulnerable, cannabis use may be associated with increased prevalence for serious mental illness, including psychosis. It is likely that this effects only a relatively small number of people with pre-existing vulnerabilities: modelling by the Global Burden of Disease Project suggested that the potential influence of cannabis use on risks for psychosis was not a major contributor to population level disease burden (Degenhardt et al, 2013).

Similarly, studies have also noted that escalating prevalence and frequency of cannabis use that has occurred in multiple countries since 1970 have not been accompanied by rises in the prevalence of serious mental illness (Degenhardt et al, 2003). More recent research has indicated that harmful effects of cannabis on risks of SMI may be limited to forms of cannabis that have low levels of cannabidiol, a cannabinoid that may be protective across multiple domains (di Forti et al, 2019).

This suggests two approaches to reducing the mental health harms of cannabis use: educational efforts to limit cannabis use among those who may be at risk for the development of psychosis (e.g., with a known family history, or those experiencing prodromal symptoms), coupled with information and increased availability of cannabis products with high levels of cannabidiol (Curran et al, 2016).

Additional interventions should focus on delaying the age of onset and reducing tobacco related routes of administration and exploring the utility of online interventions and guidelines on use (e.g. drugsmeter.com and saferuselimits.co developed by GDS and freely available).

2. What evidence is there on the ways in which people are educated on the effects of cannabis?

In the US, consumers increasingly view cannabis as harmless and lack education on its negative effects, e.g. in relation to prenatal exposure, impaired driving and vehicle crashing (Hasin et al, 2018). In the UK, there is press coverage of variable quality/accuracy, often focused on mental health. In schools in the UK there is very variable educational provision on drugs. Recent work by Global Drug Survey from 55.000 cannabis users supports the use of health warnings/ advice labels in a regulated market (<https://www.globaldrugsurvey.com/gds-2019/gds2019cannabis-health-information-labels-why-its-time-to-have-mandatory-warnings-as-part-of-any-legal-cannabis-market-and-how-theyll-help-keep-the-cannabis-industry-on-the-straight/>).

## Part 1J: Research

1. What do you think are the top two priorities for researchers looking into the relationship between cannabis and mental health?

1. With recent changes in medical cannabis policy here and recreational cannabis policy/ supply internationally, firstly, there MAY be changes in the nature of cannabis use (e.g., increased use of vaping and edibles as a route of administration, increased availability of concentrates/BHO); secondly, there WILL be occasional 'panics' about increased use/harms based on flimsy/non-existent data. Therefore, there should be a systematic attempt both to collate existing data and supplement this with additional data to track cannabis use and cannabis markets.
2. As most use is initiated in adolescence when the eCB system plays a major role in neurodevelopmental and maturational processes there is a need for research to differentiate between adolescents and adults in studying the effects of cannabis on the brain & mental health.

There is also a general need for greater surveillance of cannabis markets/patterns of use. Relative to the US and the Netherlands, which have extensive annual data collections on patterns of cannabis (and other drug use) among general population and youth samples, there is little information available here. Similarly, there should be a systematic approach to collecting/ collating data on types/ potency/ availability of different cannabis products.

## Part 1K: Other comments

1. Is there anything you would like to add to the above, or any other key areas the Review should be focussing on?

## **Part 2: Medicinal Cannabis**

### Part 2A: Medicinal cannabis products for mental illnesses

1. How strong is the evidence-base for cannabis-based medicinal products for use to treat mental illness? *When presenting your evidence, please clarify what mental disorder and what treatment you are referring to.*

There are multiple strains of cannabis which differ widely in their many constituent cannabinoids and terpenoids. We are only just beginning to understand the complexities of interactions between these constituents (Russo and Marcu, 2017) and expanding this knowledge will be crucial in facilitating the development of new cannabis derived medicines.

These two cannabinoids have a range of opposing effects on the human brain and behaviour. For example,  $\Delta^9$ -THC acutely impairs learning, produces psychosis-like effects and increases anxiety (D'Souza et al, 2004), whereas CBD can enhance learning (Das et al 2013) and has antipsychotic (Leweke et al 2012; McGuire et al, 2017) and anti-anxiety (Bergamaschi et al 2011) properties in humans. When taken together, CBD may ameliorate some of the harmful effects of  $\Delta^9$ -THC (e.g. Morgan et al, 2010a,b; Englund et al, 2013).

CBD appears to buffer the user against some of the acute effects of THC on the brain (Wall et al, 2019). This study showed that a cannabis strain containing 8mg THC without CBD impaired functional connectivity in the brain's default mode (particularly in the posterior cingulate area) and salience networks, while a strain with the same dose of THC plus 10mg CBD caused only a minimal disruption to these regions, suggesting that CBD counteracts some of THC's effects. The salience network supports other brain networks and determines what sensory or emotional inputs we pay attention to, and disruptions of the network have previously been implicated in both addiction and psychosis. Indeed, in accordance with these effects, we previously found that CBD in cannabis acutely reduced the salience of cannabis-cues in recreational users (Morgan et al, 2010a). If CBD can restore disruption to the salience network, this could be a neuroprotective mechanism which could explain its potential to treat disorders of salience such as psychosis (Leweke et al 2012; McGuire et al, 2017) and addiction (Curran et al, 2016).

Addiction/dependency. There has been an increase in numbers of young people entering treatment for cannabis dependency (EMCDDA, 2018; Freeman et al, 2018) but so far, there is no effective pharmacological treatment for cannabis dependency which is clearly an unmet need. CBD may potentially offer such a treatment. There is some evidence that CBD can reduce the number of cigarettes people report smoking (Morgan et al, 2013) so it might be worth evaluating CBD in a range of substance use disorders. Moreover, there is promising research showing that CBD has the potential to reduce cue-induced craving and anxiety in opioid users (Hurd et al, 2019), providing a strong basis for further investigation of this phytocannabinoid as a treatment option for opioid use disorder.

PTSD. The rationale for developing cannabis-based medicines for PTSD rests on a number of observations. The considerable coexistence of PTSD and cannabis use (Hasin et al, 2016) suggests some patients use cannabis in a form of 'self-medication', which is confirmed in experiential studies (Boden et al, 2013). Cannabinoid administration in animal models reduces PTSD-like behavioural responses (Zer-Aviv, 2016), and placebo-controlled studies in healthy volunteers indicate that cannabidiol administration can reduce features of anxiety (Das et al, 2013). Neuroimaging suggests that PTSD is associated with upregulation of CB1 receptors and altered anandamide signalling (Neumeister, 2013). However, only one placebo-controlled study of a cannabinoid preparation (nabilone) indicating potential benefit in patients with PTSD has been published, and it has limitations including small sample size, cross-over design, and efficacy only in some symptom domains (Jetley et al, 2015).

'Experimental medicine' studies in healthy volunteers, based on the trauma film paradigm, have demonstrated the effects of medications in reducing target psychological symptoms (Kamboj et al, 2019). If a cannabinoid preparation reduced intrusive memories and psychological distress in such a study, this would provide encouraging 'proof-

of-concept' information, and extend the rationale for subsequent randomised placebo-controlled trials.

1. What action, if any, do you think should be taken by governing bodies and clinicians to reflect this evidence-base?

DrugScience believes that the best way to accelerate medical cannabis research is through setting up a series of expert networks in specific disorders. In these specialists will conduct clinical outcome audits of specific cannabis products on defined patient groups with standardized inclusion criteria and outcome ratings. This would be much faster and cost effective than conventional clinical trials. Support for project managers for such networks should be provided e.g. by NIHR.

## Part 2B: Guidance on medicinal cannabis

1. What guidance is required for clinicians on how they should prescribe medicinal cannabis in the UK, especially in relation to possible adverse mental health effects and also other effects including impaired driving ability?

Physicians are often reluctant to prescribe an unlicensed medicine. Doctors lack the knowledge of cannabis medicine to have the confidence to prescribe: they have not been trained in prescribing it and may not know the dosage etc. This barrier can be overcome by developing an educational programme, e.g. by Health Education England.

A priority should be to provide a range of good quality teaching programmes, including a focus on mental health effects (both positive and negative). The Academy of Medical Cannabis (see [taomc.org](http://taomc.org)) now provides a free 12 module programme on the basics of cannabis which has now been used by about 1000 doctors. Further developments should include a diverse range of other teaching possibilities, such as one day seminars and more detailed, accredited, certificate course programmes as well as university courses for undergraduate doctors and other health professionals, including specific modules on medical cannabis and mental health.

There will be further challenges for prescribers/pharmacists that need to be addressed, and regularly revised guidelines for prescribers will need to be issued, as e.g. in Canada ([http://www.cpsa.ca/wp-content/uploads/2018/05/AP\\_Cannabis-for-Medical-Purposes.pdf](http://www.cpsa.ca/wp-content/uploads/2018/05/AP_Cannabis-for-Medical-Purposes.pdf)).

The current evidence suggests cannabis [and hence medical cannabis] carries a relatively low risk for driving but this is dose-related and the situation should be monitored (Wolff et al, 2013). A study in Canada found no evidence of increased crash risk in drivers with THC<5ng/mL and a statistically non-significant increased risk of crash responsibility (OR=1.74) in drivers with THC≥5ng/mL (Brubacher et al, 2019). Patients using medical cannabis should be advised, like they would be with other medicines, that they should not drive if they feel impaired in any way.

## Part 2C: Research into medicinal cannabis

1. What research is needed into the use of medicinal cannabis for treating mental illness?

Lots – many areas – a priority is to determine which patients groups are using and benefitting from use of cannabis sourced from black market at present and more systematically gather evidence in these groups. RCTs are clearly important but other research strategies such as experimental medicine approaches should also be employed.

2. What barriers are in place preventing research into medicinal cannabis for use for mental illness?

Major barriers include access and availability of different formulations and resistance from CCGs to allow prescribing. A further barrier is the pharmaceutical industry's lack of large scale funding to date.

3. How can these barriers be overcome?

Barriers can be overcome by a) top down encouragement from government and department of Health, and b) bottom up pressure from patient groups and partnerships of interested Health Professionals.

## Part 2D: Link between medicinal cannabis and recreational use

1. What evidence is there internationally of a link between the prescription of medicinal cannabis and the prevalence of recreational use?

In their US review, Hasin et al 2018 found that medical cannabis laws and their specific provision did not lead to an increase in adolescent cannabis use. However, limited evidence suggests that medical cannabis laws in the US might be associated to an increase in cannabis potency and adult cannabis use. The evidence base is still developing and there is an urgent need for further research into if and what impact medical cannabis prescriptions might have on the prevalence of recreational use.

#### Part 2E: Pathways in and out of cannabis for medicinal use

1. What evidence is there for people's pathways into use of medicinal cannabis and their pathways to continued use and out of its use?

There is currently a lack of evidence, GDS2019 has the required data but this has not yet been analysed.

#### Part 2F: Other comments

1. Is there anything you would like to add to the above, or any other key areas the Review should be focussing on?