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Clinical Guidance on Cannabis for Medical Use

1. Clinical Guidance

1.1. Aim

This Clinical Guidance will form part of the Cannabis for Medical Use Access Programme, once it has been established.

Access to authorised cannabis-based products is limited in Ireland as no cannabis-based authorised medicines are currently marketed here. Where authorised cannabis-based medicines are not available, cannabis-based products that are not authorised as medicines may be used by doctors for patients under their care, based on specific criteria. As there is limited clinical information on the use of cannabis-based products for medical purposes, this guidance aims to provide practical clinical information to healthcare professionals who are prescribing, dispensing and monitoring cannabis-based products.

The Cannabis for Medical Use Access Programme is not required or intended for authorised medicinal products but rather is to facilitate access to cannabis-based products that are not authorised as medicines but are of a standardised quality and meet an acceptable level of quality assurance during their manufacturing process.

1.2. Context and Scope

This guidance is intended for use by healthcare professionals using cannabis-based products for the treatment of patients under their care, including consultants responsible for the initiation and management of treatment, general practitioners (GPs) responsible for the continuation and monitoring of treatment, nurses responsible for the monitoring of patients, and pharmacists that dispense cannabis-based products and advise patients.

The context and the source of the clinical information on the use of cannabis-based products comes from the literature on both authorised cannabis-based medicines and cannabis-based products that are not authorised as medicines.

The target patient population includes those under the care of a medical consultant, with the following medical conditions:

- spasticity associated with multiple sclerosis resistant to all standard therapies

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- intractable nausea and vomiting associated with cancer chemotherapy, despite the use of standard anti-emetic regimens
- severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications.

Cannabis-based products are not intended as first-line treatment for these conditions.

2. Cannabis for Medical Use

2.1. Definition

Medical use of cannabis describes a situation where a doctor prescribes or recommends the use of a cannabis-based medicine or product for treatment of a medical condition in a patient under his/her care.

Dried cannabis plant material, for example, dried flowers, or products that have been manufactured from chemicals, known as cannabinoids, extracted from the cannabis plant can be used as medical treatments. Oils may also be manufactured from the extracts of the cannabis plant.

In the European Union medicines must be authorised, either by the European Medicines Agency (EMA) or by the national medicinal products regulator; the Health Products Regulatory Authority (HPRA), before they can be marketed.

2.1.1. Cannabis-based products versus authorised cannabis-based medicines

2.1.1.1 ***Cannabis-based products*** (i.e. products not authorised as medicines) can consist of dried cannabis plant material or can be manufactured from the extracts of the cannabis plant. They have not demonstrated quality, safety and efficacy, through clinical trials, and their benefit/risk profile has not been formally evaluated by regulatory authorities. Certain such cannabis-based products have however, met basic manufacturing standards for medicines.

2.1.1.2 Authorised ***cannabis-based medicines*** on the other hand, are manufactured from standardised extracts of the cannabis plant or from synthetic sources. Cannabis-based medicines have demonstrated their quality, safety, and effectiveness based on clinical trial data. They have a positive benefit/risk profile and are subject to ongoing monitoring by regulatory authorities, such as the HPRA.

2.1.2. Cannabis Composition

Cannabis contains more than 100 plant cannabinoids (phytocannabinoids). These are the biologically active constituents of the cannabis plant that bind to receptors throughout the

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body. The mechanism of action of cannabinoids is not yet fully understood; however, it is likely that these work by mimicking the effects of the body's own cannabinoids (endocannabinoids).

The main cannabinoids studied are tetrahydrocannabinol (THC) and cannabidiol (CBD), which are thought to be the most important in terms of clinical effects. THC is the main psychoactive component of cannabis. In contrast, CBD is not psychoactive.

The amount of cannabinoids (THC and CBD in particular) in a single cannabis plant varies considerably. Cannabis-based products are often referred to by their composition of THC and CBD or by the ratio of these components (Queensland Health, 2017).

2.1.3. The endocannabinoid system

The human endocannabinoid system was discovered in the 1990s, and it appears to have a regulatory effect on many bodily functions. Studies suggest that endocannabinoids play a key role in memory, mood, brain reward systems, drug addiction, and metabolic processes, such as lipolysis, glucose metabolism and energy balance.

Cannabinoid (CB) receptors are found all over the body, but appear to be most prevalent in the following areas:

- CB1 receptors — highly concentrated in brain regions related to executive function, memory, cognition, mood, pain perception, and movement. They are also found in the heart, intestines, and bladder.
- CB2 receptors — found in the spleen, tonsils, thymus gland, bones, skin, and blood (monocytes, macrophages, B-cells and T-cells).

The endocannabinoids that interact with these receptors appear to be involved in the regulation of bodily functions, such as appetite, sleep, pain, and inflammation, and they may have a protective role in relation to brain function (Queensland Health, 2017).

Cannabinoids found in the cannabis plant (phytocannabinoids) and synthetic cannabinoids also interact with these receptors; therefore, the use of cannabis for medical purposes is plausible.

In recent years, there has been considerable interest in cannabis and cannabinoids for the treatment of human diseases, through modulation of the endocannabinoid system and potentially other systems, though the mechanism of action is not fully understood. The psychoactive effects of cannabis are caused by THC through activation of CB1 receptors. CBD has a very low affinity for these receptors (100-fold less than THC), and when it binds it produces little to no effect (Borgelt et al 2013, www.drugabuse.gov). Consequently, CBD

does not appear to have psychoactive effects. The action of CBD on other brain pathways may be relevant to its therapeutic effects.

2.1.4. Pharmacokinetics and Pharmacodynamics

Following administration, cannabinoids are distributed throughout the body. They are highly lipid soluble and accumulate in fatty tissue. THC and CBD may be stored for as long as four weeks in the fatty tissues, from which they are slowly released at sub-therapeutic levels back into the blood stream, then metabolised and excreted via the urine and faeces. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination half-life (up to 36 hours).

THC and CBD are metabolised in the liver through the cytochrome P-450 enzyme system (CYP-450); therefore, they could potentially interact with other medicines metabolised by this pathway (see section 3.9)

Cytochrome P-450 2C9 is the main enzyme responsible for the breakdown of THC to its active metabolite. Cytochrome P450-3A is also involved in its metabolism. It may take up to five days for 80 to 90 per cent of the total dose to be excreted; therefore, THC is often found in the urine many days after ceasing cannabis use.

CBD is absorbed after oral administration and reaches peak concentrations in plasma within three hours. It has a high volume of distribution and long half-life (18 to 32 hours). It is metabolised through the CYP 3A and CYP2C systems (ref CPT Feb 2017).

Though there have been no recorded deaths directly attributable to acute toxicity of cannabis in humans, in animals the median lethal dose of THC has been estimated to be >800 mg/kg (Queensland Health, 2017).

Oral doses of CBD of 600mg appear to have been tolerated safely by humans (Reddy, 2017). However, this is not recommended clinically as a maximum tolerated dose and appropriate monitoring should be conducted.

2.1.5. Summary of Efficacy and Safety

To date, three cannabis-based medicines are authorised in some countries worldwide (nabiximols, nabilone, and dronabinol), but there is limited scientific data demonstrating the efficacy and or effectiveness of other cannabis-based products for medical use.

The safety of cannabis as a medical treatment is also not well characterised. In particular, there is insufficient information on its safety during long-term use for the treatment of chronic medical conditions.

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The HPRA report (http://health.gov.ie/wp-content/uploads/2017/02/HPRA-Report-FINAL.pdf) noted that cannabis and cannabinoids have been studied in a wide variety of medical conditions over many years, but the quality of the evidence reported thus far is limited for many indications. Moreover, researchers consistently cite the need for formal placebo-controlled clinical trials to evaluate the benefits and risks of treatment. In some cases, authors differ on their views on the quality of the evidence.

A major limitation of cannabis studies is that a number of different formulations of cannabis have been used. Most studies use cannabis-based medicines; however, some studies have used cannabis-based products, such as cannabis extract. Evidence of potential effectiveness is likely to be specific to a particular cannabis formulation and will depend on variables, particularly the THC to CBD ratio. Effectiveness of a particular cannabis-based medicine or product in one medical condition will not necessarily imply that it will be effective in another medical condition.

The effectiveness of cannabis as a medical treatment also depends on the individual or patient population studied. Patients using cannabis-based medicines or products often have complex health needs, are being treated with other medicines that may interact with cannabis, and require careful medical supervision.

For these reasons, it is challenging to draw conclusions regarding the effectiveness of cannabis treatment. However, the HPRA report concluded that there is some scientific evidence to support the use of cannabis or cannabinoids as a medical treatment in patients with certain medical conditions for whom available treatments were unsuccessful.

2.1.6. Indications

Following publication of the HPRA report in February 2017, the Minister for Health accepted the proposals in the report that cannabis-based products should be made available to patients who are under the care of a medical consultant and have been diagnosed with the following medical conditions:

- spasticity associated with multiple sclerosis resistant to all standard therapies
- intractable nausea and vomiting associated with cancer chemotherapy, despite the use of standard anti-emetic regimens
- severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications.

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3. Commencing Treatment with Cannabis for Medical Use

3.1. Doctor–Patient Relationship

The health and well-being of patients depends upon a collaborative effort between the doctor and the patient that is fundamental to the provision of acceptable medical care. Therefore, doctors must document that an appropriate doctor–patient relationship has been established prior to prescribing and/or endorsing cannabis for medical use for the patient.

Consistent with the prevailing standard of care, doctors should not prescribe or endorse the prescription of cannabis for themselves or a family member.

3.2. Consultant-led Care

Under the Cannabis for Medical Use Access Programme, the initial prescribing of cannabis for medical use can only be by a medical consultant in this jurisdiction. Prescribing consultants should have appropriate expertise in the treatment of the medical conditions for which the Cannabis for Medical Use Access Programme is intended.

The term endorsed by consultant describes the system where the consultant who has initially prescribed the cannabis based product supports the course of treatment and outlines the monitoring requirements on a case-by-case basis. The monitoring (to include repeat prescribing where appropriate) may be carried out by the consultant in conjunction with the patient's GP and other healthcare professionals, including Clinical Nurse and Midwife Specialists and Pharmacists.

3.3. Informed and Shared Decision Making

The doctor should use professional judgement to decide if prescribing cannabis for medical use is the appropriate treatment for the patient. Treatment is offered to the patient, who then makes an informed decision to accept the treatment or not. The doctor should discuss the risks, benefits and alternatives of the use of cannabis with the patient as well as informing them of how the Cannabis for Medical Use Access Programme operates. This should also include an explanation of the authorisation status of the product being prescribed, i.e. that they are not authorised as medicinal products.

If the patient is a minor then the patient's parent or guardian will need to consent to the treatment. Once a patient reaches the age of 16 years-of-age then the patient should be re-consented. If the patient lacks capacity to consent then the options outlined in the Assisted Decision-Making (Capacity) Act 2015 should be taken into consideration.

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3.4. The Consultation

If cannabis-based products are being considered for a patient, resistant or refractory to conventional treatments, it is essential that the doctor– patient relationship as described above is established between the patient and the consultant and between the patient and the GP (if the GP is prescribing cannabis endorsed by a consultant and/or monitoring its use).

Prior to initiation of cannabis treatment an accurate and thorough history should be confirmed by the medical practitioner (Queensland Health, 2017). This may include:

- presenting symptoms — the symptoms for which cannabis for medical use is prescribed
- medical history — in particular:
    - cardiovascular disease, liver disease and renal disease
    - medical treatments that have been tried and have failed,
    - the duration of treatments and the reasons for discontinuation
    - for cancer chemotherapy patients, current and previous systemic anticancer treatment (SACT) and their associated emetogenic risk
    - for cancer chemotherapy patients, review of antiemetics used with each previous SACT to ensure optimal antiemetic regimens have been considered
- past medical history
- psychological and psychiatric history, including:
    - history of mental illness, including any psychotic disorders
    - risk behaviours associated with drug dependence — while previous cannabis use may not be a contraindication, care should be taken to manage the risk of dependence
    - nicotine dependence (may contribute to patient smoking a cannabis-based product)
    - alcohol dependence/abuse
    - current and previous illicit drug use (see Sections 3.5.1 and 3.5.2)
- family health history, including:
    - mental health, particularly a family history of psychotic disorders
    - paranoia
    - family history of addiction
    - social history, including: social support and family support
    - child safety considerations

  - employment, especially where it involves driving or operating machinery
  - risk of falls (in older patients)
  - family responsibilities, such as caring for children
- physical examination
- clinical investigations as needed
- medication review, including:
  - other medications that might interact with cannabis (see Section 3.9)
  - risk of side effects of cannabis for medical use (see Section 3.8).
  - prior to initiation, the patients current medicines use should be reviewed to ensure the optimal anti-emetic regimen has been used in the first instance and potential drug interactions should be considered

3.5. Contraindications and Warnings and Precautions

3.5.1 Contraindications

After review of the medical history and prior to the initiation of treatment, the following contraindications should be considered (Queensland Health, 2017):

- history of hypersensitivity to any cannabinoid
- severe and unstable cardio-pulmonary disease (angina, peripheral vascular disease, cerebrovascular disease, and arrhythmias) or risk factors for cardiovascular disease — THC acts through the CB1 receptors to decrease blood pressure, increase cardiac demand and causes vasodilation
- current, active drug dependence, including illicit drugs, alcohol, and prescription medications
- breastfeeding — considerable levels of cannabinoids are likely to be present in maternal breast milk and there are potential impacts on an infant

3.5.2. Warnings and Precautions

After review of the medical history and prior to the initiation of treatment, the following should also be considered (Queensland Health, 2017):

- patients aged 18 years old and under because of the potential effects of THC on the developing brain (see Section 3.8)
- personal or family history of schizophrenia or any psychotic disorder
- severe liver or renal disease
- previous drug dependence, including illicit drugs, nicotine, alcohol and prescription medications
- cannabis should not be used if a patient is planning to become pregnant or during pregnancy unless the potential risks to the foetus and/or embryo are considered to be outweighed by the benefit of treatment. There is insufficient experience in humans regarding the effects of cannabis on reproduction. Therefore men and women of child bearing potential should take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy. Reports of pre-term labour and low birth weight have been associated with cannabis use.
- concomitant medications, especially sedatives such as opioids and benzodiazepines and medicines metabolised by cytochrome p450 isoenzymes (see Section 3.9)
- whether the patient is elderly — as metabolism in the elderly is slower it is likely they will be more sensitive to the pharmacological effects of cannabis. Treatment should therefore be initiated at low doses and titrated slowly.

3.6. The Initial Treatment Plan

The consultant should complete a comprehensive clinical assessment of the patient that identifies risk factors that will need to be addressed before initiation of treatment with cannabis for medical use (see Sections 3.4 and 3.5).

An initial treatment plan should be discussed with the patient and should address the following points (Queensland Health, 2017):

- treatment goals for cannabis use — these should be discussed with the patient and should be related to the symptoms and measurable, where possible. For example:
  - treatment-resistant epilepsy: 25% relative reduction in seizure frequency compared to baseline, with clinically meaningful improvement in epilepsy control;
  - Dravet and Lennox-Gastaut syndrome: 25% relative reduction in seizure frequency compared to baseline, with clinically meaningful improvement in epilepsy control;
  - multiple sclerosis: reduction in spasticity which in turn may result in improved pain relief in spasm, improved sleep, increased mobility, improved quality of life. The goal is clinically meaningful/significant improvement in spasticity management;
  - chemotherapy-induced nausea and vomiting: reduction in refractory post chemotherapy nausea and vomiting.

- specify the duration of treatment: for example, 3-6 months, depending on the response, and, in the case of chemotherapy-induced nausea and vomiting, for the duration of the SACT causing intractable nausea and vomiting

- risk management processes, such as frequency of dispensing. For example, weekly dispensing if there are concerns that a patient may self-escalate their dose

- monitoring arrangements — regular reviews as clinically indicated, any blood tests, specialist reviews, and other investigations (as needed) for the particular medical condition and/or symptoms being treated

- regular review of interactions with concomitant medications (see Section 3.9)

- a treatment cessation plan for situations where the medication is not helping manage the symptoms or the goals of treatment are not reached

- upon agreement of the treatment plan informed consent should be obtained. The patient should be provided with information about cannabis for medical use and advised not to drive or operate heavy machinery while starting cannabis treatment

- written consent should be obtained for data gathering purposes

The agreed plan should be documented in the patient's notes and shared in clinical correspondence, subject to the patient's consent, with the patient's general practitioner, other consultants and other healthcare professionals as required. A pro-forma should also be completed by the initial prescriber for presentation at the pharmacy to prescribe up to 6 months of the treatment regimen. The medical team should communicate with the pharmacist as required.

3.7. Cannabis-based Products and Cannabis-based Medicines

Authorised cannabis-based medicines should be used in the first instance. However, if an authorised medicine is not available or is not suitable for the patient, cannabis-based products may be considered as a treatment option.

While dosing and administration, drug interactions, and side effect information is available for authorised cannabis-based medicines, these data are very limited for cannabis-based products; therefore, information on authorised cannabis-based medicines has been provided for reference purposes.

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3.7.1. Cannabis-based Products and Cannabis-based Medicines

The information within the tables in this section is accurate as of July 2017. To ensure you have access to the most up-to-date information please access the references provided within these tables.

3.7.1. Cannabis-based Products

The cannabis-based products that are available under the Cannabis for Medical Use Access Programme are outlined in Table 1 below. The products outlined below are of a standardised quality and meet an acceptable level of quality assurance during their manufacturing process. They cannot be considered interchangeable with each other or other cannabis-based products or medicines as there is limited information available.

All cannabis-based products should be stored appropriately and out of the sight and reach of children.

Table 1. Cannabis-based products available under the Cannabis for Medical Use Access Programme for each specified medical condition

1. ***Medical condition: Spasticity associated with multiple sclerosis resistant to all standard therapies*** **Symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.**

CANNABIS-BASED PRODUCTS PERMITTED UNDER THE ACCESS SCHEME:	≥80% purity full spectrum oral solution THC 10: CBD 10 (1:1) ≥80% purity full spectrum oral solution THC 25: CBD 25 (1:1)

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2. *Medical condition: Intractable nausea and vomiting associated with cancer chemotherapy, despite the use of standard anti-emetic regimes*	
Patients experiencing nausea and vomiting associated with highly emetogenic chemotherapy for which other medications suitable to the level of emetogenicity of the chemotherapy have not been helpful. *Consult with the medical team overseeing the SACT component to determine emetogenic risk or refer to sources for emetogenic risk of SACT e.g. National Cancer Control Program chemo regimens available at www.hse.ie/chemoregimens or international reference sources (ASCO, MASCC, ESMO etc).* Prior to initiation of cannabis treatment, review antiemetics used with each previous SACT to ensure optimal antiemetic regimens have been considered.	
CANNABIS-BASED PRODUCTS PERMITTED UNDER THE ACCESS SCHEME:	>80% purity full spectrum oral solution, THC 10mg/ml : CBD 10mg/ml >80% purity full spectrum oral solution, THC 25mg/ml : CBD 25mg/ml >80% purity full spectrum oral solution, THC 10mg/ml (CBD 0.2mg/ml) >80% purity full spectrum oral solution, THC 25mg/ml (CBD 0-4mg/ml) Vaporised formulation 19% THC: <1% CBD Vaporised formulation 12% THC: <1% CBD **(Vaporisation should be reserved for the rare instances where oral route of administration is not possible.)**
3. *Medical condition: Severe epilepsy where the severity and frequency of seizures are significantly impacting on quality of life and that has failed to respond to 5 or more standard antiepileptic treatments.*	
Severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications.	
CANNABIS-BASED PRODUCTS PERMITTED UNDER THE ACCESS SCHEME:	≥98% purity Purified oral solution (high CBD : trace THC)

In the absence of dosage information, the general recommendation is to **'start low and go slow'**. This is the pragmatic approach taken in guidance issued by Queensland Health, Australia (2017).

Specific recommendations are:

- commence treatment at the lowest possible dose
- first doses should be given in the evening to assist with management of side effects, and the patient should be advised to have someone with them
- the dose should be titrated up slowly, at intervals of between 1 and 4 weeks, until a satisfactory dose is reached
- monitor carefully for side effects upon initiation and on an ongoing basis.

Doses depend on the type of product used, individual variation, the development of tolerance, interaction with other drugs and previous exposure to cannabis, either recreationally or medically. Lower doses are less likely to be associated with side effects.

3.7.2. Cannabis-based Medicines

3.7.2.1. Spasticity Associated with Multiple Sclerosis, Resistant to other Treatments

Sativex® (nabiximols) is authorised as a medicinal product in Ireland, but not currently marketed by the company.

Product	**Formulation details**	**Dose**	**Reference**
Sativex® (nabiximols) Oromucosal spray (GW Pharma)	Each 100 microlitre spray contains: 2.7 mg delta-9 tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).	A titration period is required to reach optimal dose, starting with one spray in the pm and increasing to a maximum dose of 12 sprays per day (5 sprays: am, 7 sprays: pm). The median dose in clinical trials was 8 sprays per day.	More information can be found in the Summary of Product Characteristics available on the HPRA website. Product information is continually updated.

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3.7.2.2. Nausea and Vomiting Associated with Chemotherapy

Nabilone is authorised in the UK, Austria and the US. Dronabinol is authorised in Germany and the US (in Ireland, a Minister's licence is required for prescribing).

Product	**Formulation Details**	**Dose**	**Reference**
Nabilone 0.25 or 1 mg Capsules (Meda Pharmaceuticals)	synthetic cannabinoid - THC	The usual adult dosage is 1mg or 2mg twice a day. To minimise side-effects, it is recommended that the lower starting dose is used and that the dose is increased as necessary. The first dose should be administered the night before initiation of chemotherapy, and the second dose should be given one to three hours before the first dose of chemotherapy is administered. The maximum daily dose should not exceed 6 mg, given in three divided doses.	More information can be found on the Medicines and Healthcare Products Regulatory Agency website Product information is continually updated.
Marinol® (dronabinol) 2.5, 5 or 10 mg capsules for oral administration	synthetic delta-9-tetrahydrocannabinol (delta-9-THC)	In the clinical trials, the majority of patients were treated with 5 mg/day MARINOL® Capsules, although the dosages ranged from 2.5 to 20 mg/day. Most patients respond to 5 mg three or four times daily.	More information can be found on the Food and Drug Administration website. Product information is continually updated.

3.7.2.3. Treatment-resistant epilepsy

No cannabis-based medicines are currently authorised for this indication.

Preclinical evidence and limited clinical data suggest that cannabidiol (CBD), without THC, is the preferred treatment for epilepsy (Berkovic, 2017).

A preliminary report from an open-label study initiated by investigators to assess the safety and dosing of a purified cannabis extract containing 99% CBD and 0.1% THC (the medicinal product was Epidiolex®), reported that among 137 patients with treatment resistant epilepsy

who had received at least 12 weeks of treatment, the median reduction in the number of seizures was 54% (Devinsky at al., 2015).

A recent double-blinded, placebo controlled trial has shown that CBD (Epidiolex®) reduced the frequency of convulsive seizures among children and adults with Dravet syndrome (a severe myoclonic epilepsy of infancy) over a 14-week period; however, it was associated with higher rates of adverse events (see section 3.8.1). The percentage of patients who became seizure-free was 5% with CBD and 0% with placebo. There was no significant reduction in non-convulsive seizures (for example, brief staring spells); therefore, the authors suggest that the anti-seizure effect of cannabidiol may be specific to convulsive seizures in Dravet syndrome or that the frequency of non-convulsive seizures cannot be reliably counted by parents in developmentally delayed children. Additional data are needed to determine the long-term efficacy and safety of CBD for the treatment of Dravet syndrome (Devinsky et al., 2017).

Randomized clinical trials of Epidiolex® are now being conducted for the treatment of the Lennox–Gastaut syndrome, a childhood-onset, treatment-resistant epilepsy characterized by multiple types of seizures and developmental delay (Friedman and Devinsky, 2015).

The Clinical Advisory Group of the Health Service Executive's National Clinical Programme for Epilepsy (2017) issued a statement acknowledging that there is emerging evidence for the use of pure CBD in certain forms of severe epilepsy but cautioned that no other cannabis derivatives or products have been adequately studied to a level that they are proven to be effective and safe to use in clinical practice. Specifically, products containing THC (a cannabis derivative with potentially harmful psychoactive effects) remain inadequately tested'.

Product	**Formulation Details**	**Dose**	**Reference**
Epidiolex® (GW Pharma)	100 mg/ml sesame oil based solution. 99% pure oil based cannabidiol extract of constant composition	Severe intractable, childhood onset treatment resistant epilepsy: 2-5 mg/kg* per day as twice-daily dosing (adjunctive treatment). Uptitrated by 2-5 mg per week until intolerance or a maximum dose of 25 mg/kg/day. Some sites permitted	Devinsky et al, 2015

		50 mg/kg/day	
Epidiolex® (GW Pharma)	100 mg/ml sesame oil based solution. 99% pure oil based cannabidiol extract of constant composition	Dravet Syndrome: dose escalation over 2 weeks up to 20 mg/kg/day, administered twice daily and a 10-day taper period. *	Devinsky et al, 2017

*Starting doses of as low as 0.5 mg/kg/day may be better tolerated by some patients (Devinsky, verbal communication to the Expert Group). In rare cases, as with other anti-epileptic medications, seizures may worsen during treatment with cannabis for medical use.

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3.7.3. Route of administration and pharmacology

The pharmacology of cannabis varies depending on the route of administration. The oral route, vaporising, smoking, and oro-mucosal sprays are considered. While smoking and oromucosal sprays are not recommended as part of the programme, the information provided below should be considered (Queensland Health, 2017).

Oral route

Cannabis-based medicines consumed in the oral form, such as oils or liquid capsules, are more slowly absorbed than products administered by vaporising. They take at least 30 to 90 minutes before any effects are felt. Bioavailability of oral cannabinoids is lower (10 to 20 per cent) because of intestinal and first pass liver metabolism.

Peak effects can occur two to four hours after consumption. Given the longer time frame for peak effects, it is important to allow at least three hours between administration of single oral doses to avoid possible overdose. Effects can last for up to eight hours and as long as 24 hours. This may be of particular importance in relation to the timing of SACT in order to get the maximum benefit

Given the slower onset and longer duration, it is expected that taking cannabis-based products via the oral route would be more useful for medical conditions or symptoms where control over longer periods of time is sought — similar to the use of slow release medications (Queensland Health, 2017).

Vaporising

Vaporised cannabis results in rapid absorption and high blood levels, similar to smoking it.

Cannabis is heated at a lower temperature than smoking, producing fewer toxins and no side stream smoke', making passive smoking less of a problem. First effects occur within 90 seconds and reach a maximum after 15 to 30 minutes, before wearing off after two to four hours.

Vaporising heats the cannabis without burning it and releases the cannabinoids in the form of a vapour, which is then inhaled. Given the rapid onset of action, vaporising cannabis-based products is best for symptoms or conditions where rapid relief is required. The amounts of THC and other cannabinoids delivered by the vaporiser are dependent on the temperature, the duration of the vaporisation and the volume of the balloon in the vaporiser (Queensland Health, 2017). This may pose difficulties for dose titration. The health effects of vaporising as a route of administration for cannabis products are as yet unknown.

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Smoking

Smoking is **not recommended** as a method of administration of cannabis for medical purposes due to the potential other risks associated with smoking, including cardiorespiratory illnesses and cancer. **The access programme does not include any products intended to be smoked.** Most carcinogens in smoked tobacco are present in smoked cannabis. Typical cannabis use results in a larger volume of smoke being inhaled than with ordinary tobacco products and a fivefold increase in concentrations of carboxyhaemaglobin (Winstock et al, BMJ, 2010).

Oro-mucosal sprays

Information on the administration of nabiximols, an oro-mucosal spray, is in the authorised product information https://www.hpra.ie/homepage/medicines

3.8. Side Effects

3.8.1. Cannabis-based Medicines

Information on the side effects of cannabis-based medicines comes from clinical trials and is available in the published product information.

Nabiximols (Sativex®) contains THC and CBD in a 1:1 ratio. The most commonly reported adverse reactions in the first four weeks of exposure were dizziness, which occurs mainly during the initial titration period, and fatigue. These reactions are usually mild to moderate and resolve within a few days even if treatment is continued. Common side effects include gastrointestinal disorders such as a change in appetite, constipation, diarrhoea, and vomiting; psychiatric disorders, including depression, disorientation, dissociation, and euphoria; and nervous system disorders, including amnesia, disturbances in balance and attention, and somnolence.

The most common side effects associated with nabilone (synthetic cannabinoid, THC analogue) include drowsiness, vertigo/dizziness, euphoria, dry mouth, ataxia, visual disturbance, concentration difficulties, sleep disturbance, dysphoria, hypotension, headache, and nausea.

The commonest side effects associated with dronabinol (synthetic cannabinoid, delta-9-THC analogue) include nervous disorders such as dizziness, euphoria, paranoid reactions, somnolence, and abnormal thinking as well as gastrointestinal disorders such as abdominal pain, nausea and vomiting.

Cannabidiol (CBD) is not an approved medicine in any country. A recent double-blinded, placebo controlled trial has shown that among patients with Dravet syndrome, CBD (Epidiolex®) resulted in a greater reduction in convulsive-seizure frequency than placebo; however, this was also associated with higher rates of adverse events. Of those treated with CBD, 93% reported an adverse event and although 84% were considered mild/ moderate, eight of the sixty patients treated with CBD discontinued due to side effects compared to one patient in the placebo group. Adverse events that occurred more frequently in the CBD group than the placebo group included diarrhoea, vomiting, fatigue, pyrexia, somnolence and abnormal results on liver-function tests. Some effects of CBD may relate to interactions with other antiepileptic drugs (see section 3.9). Serious adverse events were more common in the CBD group than the placebo group (16% vs 5%) (Devinsky et al 2017 and Berkovik 2017). If Epidiolex® is authorised as a medicine in the future, the published product information should be consulted.

3.8.2. Cannabis-based Products

Much of the information on safety of cannabis-based products comes from epidemiological studies which have been conducted on recreational drug use. In the majority of studies, there is little information on the THC and CBD content of cannabis, which is a significant limitation given the different pharmacological properties of these cannabinoids. The limitations of the research need to be considered in determining whether the associations described between cannabis use and the development of safety risks are causal.

The short-term effects of cannabis use are reasonably well understood and include (Adapted from Volkow et al, 2014):

- Euphoria, hallucinations, anxiety, paranoia and psychosis
- Impaired short-term memory and confusion, making it difficult to learn and retain information
- Impaired motor co-ordination, interfering with driving skills and increasing the risk of injuries
- Altered judgement, increasing the risk of sexual behaviours that facilitate the transmission of sexually transmitted diseases.

The effects related to long term, repeated use of cannabis are where the greatest concerns and main uncertainties lie. Cannabis addiction, psychosis, and neurocognitive effects are predominantly linked to the THC component. Side effects of long term or heavy use of cannabis include (adapted from Volkow et al, 2014):

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- Addiction (in 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)
- Increased risk of chronic psychosis disorders (including schizophrenia) particularly in adolescents and persons with a predisposition to such disorders
- Cognitive impairment, with lower IQ among those who were frequent users during adolescence
- Altered brain development
- Poor educational outcome, with increased likelihood of dropping out of school
- Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general populations)
- Increased risk of suicidal ideation and attempt
- Symptoms of chronic bronchitis related to smoked cannabis

The diagram describes the link between cannabinoids and psychosis (Figure 1). The primary psychotogenic component of cannabis is THC, although other cannabinoids may also be psychoactive. CBD is reported to possess anxiolytic and antipsychotic properties, and is thought to have a neuroprotective role, as it may counteract or moderate some of the side effects induced by THC (Rabin & George, 2017).

Critical neurodevelopmental processes occur up to the age of 18. Therefore, cannabinoid use in adolescence may be more toxic compared to use introduced in adulthood. Because cannabis is not sufficient to cause schizophrenia by itself, genetic factors likely play a role in mediating the development of the disorder. Chronic use and high-potency cannabinoids are risk factors that further increase the likelihood of psychotic symptoms and progression to chronic psychosis (Rabin & George, 2017).

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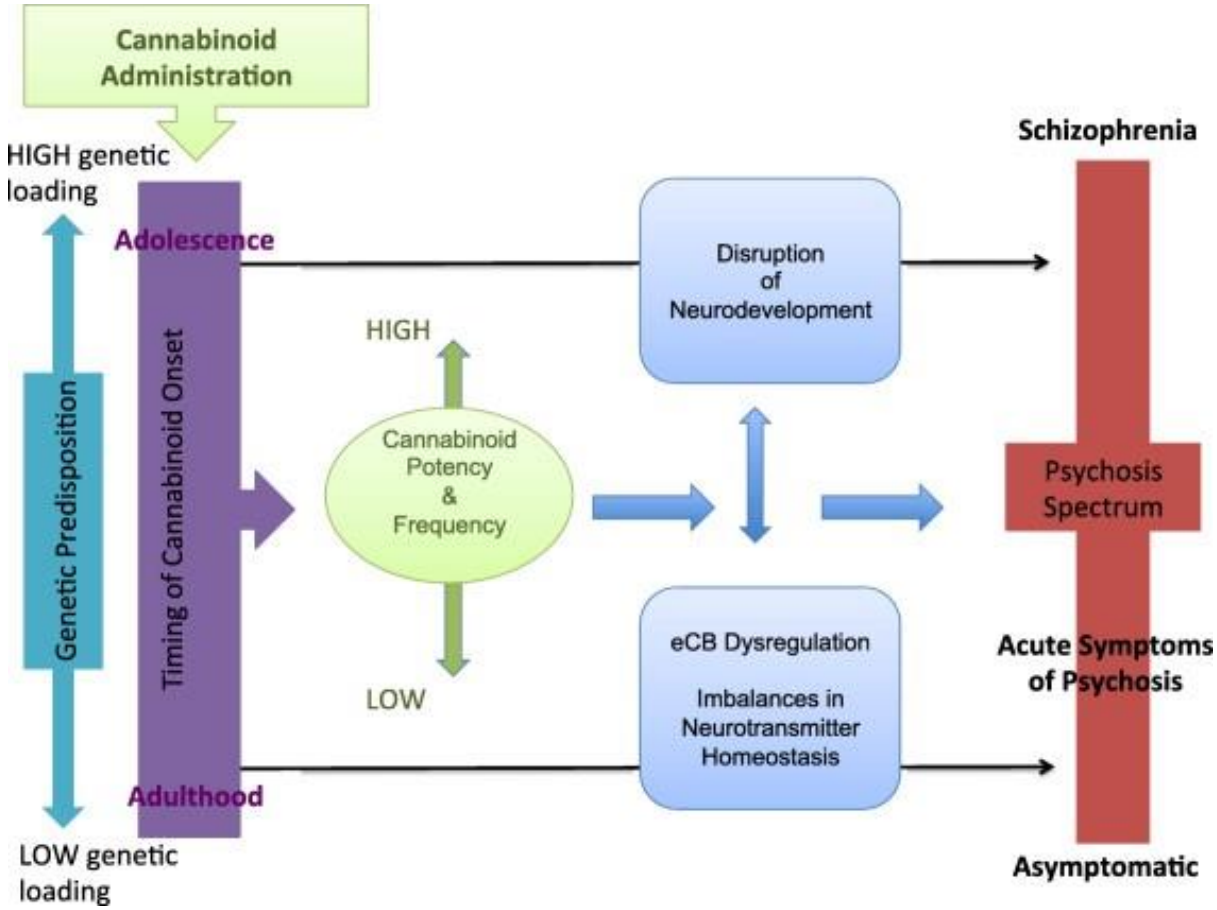
Figure 1: Risk factors and pathways to psychosis.



3.9. Potential Interactions with Medicines and Other Interactions

Caution should be exercised when prescribing or dispensing cannabis for medical use due to the potential for interactions with medicines including non-prescription medicines, herbal medicines, or food supplements. A full review of concomitant medicines and supplements should be conducted prior to prescribing and dispensing cannabis for medical use. Reliable medicines interaction resources can be referenced.

Drug interaction information available for authorised cannabis-based medicines is summarised below; however, it is recommended that the product information for each medicine is consulted as this information is updated on a regular basis.

Regarding cannabis-based products, due to the limited available information in humans on the drug interaction profiles of THC and CBD and based on their pharmacodynamic and

pharmacokinetic profiles, the potential for drug interactions with other medicines should be considered.

3.9.1. Potential Interactions Relevant to the Indications Included in the Cannabis for Medical Use Access Programme

There is a possibility of a clinically significant interaction between concomitant medicines and cannabis-based products.

Care should be taken with hypnotics, sedatives, and medicines with potential sedating effects as there may be an additive effects on sedation and muscle relaxing effects.

Care should be taken when co-administering cannabis-based products with anti-spasticity agents as a reduction in muscle tone and power may occur, leading to a greater risk of falls. A potential for interaction between cannabis for medical use and disease modifying treatments for multiple sclerosis should be considered.

CBD can interact with other epilepsy medicines, causing levels of those medicines in the blood to rise. This means that patients should be carefully monitored for side effects and to ensure that their drug levels remain therapeutic and do not enter the toxic or harmful range. For example, elevated levels of clobazam, and its active metabolite have been reported in children with refractory epilepsy treated with CBD (Geffrey et al, 2015). Therefore, monitoring of clobazam levels is necessary for the clinical care of patients concomitantly treated with clobazam and CBD.

Other interactions of relevance are detailed below and in Table 2.

3.9.2. Potential effects of cannabis-based products on other medicines

The information provided within this section is not exhaustive.

Both THC and CBD inhibit the CYP2C family of isoenzymes at low concentrations.

Examples of medicines metabolised by these enzymes include repaglinide, celecoxib, warfarin, lansoprazole, omeprazole (Stout and Cimino 2014) diclofenac, ibuprofen, naproxen, diazepam andcitalopram (NMIC Drug Interactions 1: How they occur, Bulletin 2008;14:4).

Both THC and CBD inhibit CYP3A4 at higher concentrations. Examples of medicines metabolised by these enzymes include alfentanil, everolimus, midazolam, simvastatin, triazolam, vardenafil (Stout and Cimino 2014), atorvastatin, clarithromycin, erythromycin, ketoconazole, oestradiol and progesterone (NMIC bulletin 2008;14:4), aprepitant, voriconazole and itraconazole

THC and CBD possibly induce CYP1A2 (Stout and Cimino, 2014). Examples of medicines metabolised by this enzyme include duloxetine, melatonin, theophylline, tizanidine (Stout and Cimino 2014), amitriptyline and warfarin (NMIC bulletin 2008;14:4).

Co-administration of a cannabis tea (18% THC and 0.8% CBD) has been reported not to interact with intravenous irinotecan and docetaxel administered to cancer patients (Engels et al, 2007).

It is stated in the product information for nabiximols (Sativex) that the in vitro inhibitory effects of nabiximols on CYP3A4, and CYP2C19 occur at concentrations substantially higher than the maximum observed in clinical trials. No interactions with at risk-CYP3A4 medicines are therefore expected.

3.9.3. Potential effects of other medicines on cannabis-based products

Concomitant treatment with CYP3A4 inhibitors, such as ketoconazole, can increase the Cmax and AUC of THC, its main metabolite, and CBD. Therefore, if concomitant treatment with CYP3A4 inhibitors (for example, itraconazole, ritonavir, and clarithromycin) is started or stopped during treatment with cannabis for medical use, a new dose titration of the cannabis-based products for medical use may be required.

Following treatment with the CYP3A4 inducer rifampicin, reductions in Cmax and AUC of THC, its primary metabolite, and CBD have been observed. Therefore, concomitant treatment with strong enzyme inducers (for example, rifampicin, carbamazepine, phenytoin, phenobarbital, and St John's Wort) should be avoided whenever possible. If deemed necessary, careful titration is recommended, notably including within the two weeks following the discontinuation of the inducer.

Topiramate is an inhibitor of CYP2C19. Sodium valproate is reported to inhibit CYP2C9 and CYP3A4. Therefore, the potential for interactions between anti-epilepsy medicines and cannabinoids is bidirectional (Friedman & Devinsky, 2015).

Clinical pharmacogenetic data support CYP2C9 as a significant contributor to THC metabolism (Stout & Cimino, 2014).

Further interactions are detailed in Table 2.

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Table 2. A list of possible interactions with cannabis (Adapted from Katz et al., 2017). NOTE: This list is not exhaustive.

Group	**Examples of Medicines**
Alcoholic beverages and medicines used in alcohol dependence	Naltrexone
Amphetamines	
Anti-anxiety, hypnotics and sedatives	Barbiturates Narcotic analgesics including codeine and morphine Benzodiazepines including clobazam, diazepam and triazolam Duloxetine
Anti-coagulants	Warfarin
Anticholinergic	Atropine Ipratropium
Anti-depressants	Selective serotonin reuptake inhibitors, for example, fluoxetine; tricyclic antidepressants and amitriptyline.
Anti-epileptics	Clobazam Carbamazepine Eslicarbazepine Midazolam Phenytoin Phenobarbital Sodium valproate Topiramate Zonisamide
Anti-infectives	Ketoconazole Itraconazole Clarithromycin Rifampicin Erythromycin
Anti-psychotics	Chlorpromazine
Anti-spasticity, muscle relaxants	Baclofen Tizanidine
Herbal medicines	St John's Wort

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Mood stabilizers	Lithium
Non-steroidal Anti-inflammatories	Ibuprofen Naproxen
Protease inhibitors	Indinavir Nelfinavir Ritonavir
Proton pump inhibitors	Lansoprazole Omeprazole
Phosphodiesterase inhibitors	Sildenafil Vardenafil Theophylline
Statins	Atorvastatin Simvastatin
Others	Digoxin Everolimus Melatonin Oestradiol Progesterone Aprepitant

3.9.4. Interaction with alcohol

Cannabis may interact with alcohol (ethanol), affecting co-ordination, concentration and ability to respond quickly. In general, alcoholic beverages should be avoided whilst using cannabis-based medicines or products, especially at the beginning of treatment or when changing dose.

Patients should be advised that if they do drink alcohol while using cannabis the additive effects on the brain may impair their ability to drive or use machines, and increase the risk of falls.

3.10. Transferring to Another Cannabis-based Medicine or Product, Withdrawal from Treatment, and Discontinuation of Therapy

Patients transferred from one cannabis-based medicine or product to another may require to be titrated again, depending on the composition of the medicine or product. The impact of any differences in composition should be considered in terms of the potential for side effects and interactions.

The symptoms associated with the withdrawal of treatment include irritability, difficulty sleeping, decreased appetite and anxiety. Gradual withdrawal of treatment is recommended, unless abrupt discontinuation is required for safety reasons.

3.11. Effects on ability to drive and use machines

Cannabis may produce undesirable effects such as dizziness and somnolence which may impair judgement and performance of skilled tasks. Patients should not drive, operate machinery or engage in any hazardous activity if they are experiencing any significant central nervous system (CNS) effects such as dizziness or somnolence.

The Road Traffic Act 2016 provides for medical exemption certificates for patients prescribed cannabis for medical use containing THC. Prescribers and patients should familiarise themselves with the clinical and driving effects of cannabis for medical use as well as the drug testing regime in Ireland. Further information can be obtained at www.rsa.ie

3.12. Ongoing monitoring

The treatment plan for each patient should include clear definition of the treatment goals/desired endpoints and should specify regular clinical monitoring required, including the monitoring intervals and the duration of the trial period.

Patients should be reviewed regularly to monitor effectiveness and manage any side effects and potential drug interactions. Patients should be advised to record their experience of use, including any side effects observed, or views regarding the impact of treatment and to share this at the time of review. Patients should be reviewed more frequently when commencing cannabis-based products, daily if required. Once established on a dose, regular review is recommended (Queensland Health, 2017). This may include telephone management, as deemed appropriate.

Healthcare professionals and patients are encouraged to report any suspected side effects to the HPRA preferably using the online or downloadable reporting options accessible from the HPRA website (www.hpra.ie). Patients should liaise with their consultant and seek review of treatment if necessary.

Data will be collected for patients using the Cannabis for Medical Use Access Programme.

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4. Additional information

For additional information, the following sources may be of use:
Cannabis for Medical Use – A Scientific Review, February 2017 (www.hpra.ie)
Queensland Health, (2017). Clinical Guidance: for the use of medicinal cannabis products in Queensland. Available at: https://www.health.qld.gov.au
Office of Medicinal Cannabis (OMC), The Netherlands https://www.cannabisbureau.nl/english

Irish Association of Neurologists, 2017: https://www.rcpi.ie/news/releases/statement-from-the-royal-college-of-physicians-of-ireland-on-theuse-of-cannabis-products-in-the-treatment-of-severe-epilepsy-in-children-and-adults/
NMIC Drug Interactions 1: How they occur, Bulletin 2008;14:4.

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Health Products Regulatory Authority report: Cannabis for Medical Use — A Scientific Review. (2017) http://www.hpra.ie/docs/default-source/publications-forms/newsletters/cannabis-for-medical-use--a-scientific-review.pdf?sfvrsn=5

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