EVIDENCE BRIEF AND TECHNICAL DOSSIER FOR POLICY ON MEDICAL CANNABIS IN ZAMBIA

Perspective

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EVIDENCE BRIEF

Key Messages

- Medicinal Cannabis may be classified into Marijuana, with a concentration of the psychoactive substance (alters brain function) delta-9-tatrahydrocannabinol (THC) of more than 0.3% and Industrial Hemp or Cannabidiol (CBD) with a concentration of THC no more than 0.3%.
- Combinations of THC and CBD have been shown to have medicinal value for alleviating chronic pain of nerve origin, nausea and vomiting associated with cancer chemotherapy, certain types of epilepsy, loss of appetite and weight loss associated with AIDS, and some mental illnesses, such as schizophrenia.
- However, although there are some cannabis-based medicines that have been licensed for use, for example in the United States, overall, research evidence on the effectiveness of medicinal cannabis on the above conditions and other medical conditions is divided and not yet conclusive.
- Research evidence shows that side effects from cannabis with a higher THC concentration outweighs the benefits; but there is potential for use of CBD based cannabis medicines because they have fewer side effects and CBD has essentially no psychoactive effects; with little if any potential for abuse.
- One CBD based cannabis medicine, Epidiolex, is now licensed in the United States for treatment of some forms of epilepsy that are resistant to common medicines for seizures.
- There are two THC based cannabis medicines licensed in the United States. They are: Dronabinol (Marinol ®), a synthetic THC, for treatment of nausea and vomiting caused by cancer chemotherapy and loss of appetite and weight loss due to AIDS; Nabilone (Cesamet ®) also used for nausea and vomiting due to cancer chemotherapy.
- WHO ECDD Recommendations: The November, 2018 WHO Expert Committee on Drug Dependence (ECDD) (Annex 1) recommended that Cannabis and Cannabis Resin be deleted from Schedule IV of the Single Convention on Narcotic Drugs (1961); that Dronabinol (delta-9-tetrahydrocannabinol) be added to Schedule I of the Single Convention on Narcotic Drugs (1961); that Tetrahydrocannabinol (isomers of delat-9-tetrahydrocannabinol) be added to schedule I of the Single Convention on Narcotic Drugs (1961); *"Preparations containing predominantly cannabidiol and not more than 0.2 per cent of delta-9-tetrahydrocannabinol are not under international control."*

preparations considered to be pure cannabidiol (CBD) should not be scheduled within the International Drug Control Conventions by adding a foot note to the entry for cannabis and cannabis resin in Schedule I of the Single Convention on Narcotic Drugs (1961) to read:

The Problem Brief

In spite of the legal provision to allow for cultivation and dealing with cannabis for medicinal and scientific purposes, that provision has never been implemented in Zambia. The main reason for non-implementation of the law in this regard is the fact that there are no regulations to operationalize the legal provisions. Regulations have not been developed possibly due to lack of evidence on medical value of implementing a program for medicinal cannabis in Zambia.

In the recent past, the Ministry of Health (MOH) has been under pressure to issue licenses to prospective developers to cultivate Cannabis for medicinal and/or scientific purposes.

Is there strong, reliable, and conclusive evidence on the efficacy, effectiveness, and safety of cannabis for medicinal use? Is there justification for Zambia to grow Cannabis for medicinal and/or scientific use?

The key questions are:

Policy Options

1.0 Cultivate Industrial Hemp for research purposes only

What: MOH to issue licenses for cultivation of Industrial Hemp (Cannabidiol/CBD with no more than 0.2% THC) on pilot basis for scientific/ health research purposes only.

Why: Evidence shows that CBD is effective against some forms of epilepsy and may alleviate some symptoms of schizophrenia. There is however insufficient evidence for use of CBD alone for chronic pain, nausea and vomiting from cancer chemotherapy and other medical conditions. More high quality randomized controlled longitudinal clinical trials are need to have conclusive results. The potential for the medicinal value of cannabis lies in exploring the efficacy and safety of CBD because, with less than 0.3% THC, it has been shown to have no psychoactive effects. However, the current evidence on the effectiveness and safety profiles of the THC/CBD combinations is still mixed and not conclusive; but it is clear that the more THC there is in this combination, the more side effects there are.

Operational feasibility: Moderate to High. Due to the non-psychoactive nature of CBD, the chance of abuse is low and therefore, licensing cultivation of Industrial Hemp for research purposes is feasible.

Considering that according to the WHO ECDD preparations containing predominantly cannabidiol and not more than 0.2% THC are not under international control, there will be less stringent security measures for its cultivation, processing, and export.

2.0 Cultivate both Industrial Hemp and Marijuana for research purposes only

What: MOH to issue licenses for cultivation of both Marijuana and Industrial Hemp (Cannabidiol with no more than 0.2% THC) on pilot basis for health research purposes.

Why: Evidence shows that THC alone and in combination with CBD is effective against chronic pain due to nerve irritation, nausea and vomiting from cancer chemotherapy and other medical conditions.

There are currently two THC based medications licensed in the United States. However, the current evidence on the effectiveness and safety profiles of the THC/CBD combinations is still mixed and not conclusive. More high-quality randomized, controlled, longitudinal clinical trials are need to provide conclusive results.

Operational feasibility: Low. Due to the psychoactive nature of THC, the chance of abuse is very high; restricting Marijuana to health research and controlling the recreational use would be a big challenge.

3.0 Cultivate both Industrial Hemp and Marijuana for medicinal and research purposes

What: MOH to issue licenses for cultivation of both Marijuana and Industrial Hemp (Cannabidiol with no more than 0.2% THC) on full scale for both medicinal and health research purposes.

Why: Evidence shows that THC alone and in combination with CBD is effective against chronic pain due to nerve irritation, nausea and vomiting from cancer chemotherapy and for spasticity associated with Multiple Sclerosis.

Operational feasibility: Low. Due to the psychoactive nature of THC, the chance of abuse for recreational purposes is very high.In addition, other than the two epileptic conditions, which are rare in Zambia,

There is no evidence that Cannabis-based medications are better than current conventional medicines for medical conditions prevailing in Zambia.

Policy Recommendations

1.The overarching recommendation is for Zambia to implement a program for cultivation of medicinal cannabis for scientific purposes only.

2.The specific recommendation is that the Minister of Health may issue licenses for cultivation of Industrial Hemp (Cannabidiol with no more than 0.2% THC) for scientific purposes only until such a time that there is conclusive evidence to warrant cultivation on a wider scale for medical use.

3.The current legal framework should be supported by subsidiary legislation that will provide the manner and form of the licensing process as recommended by the Committee on cultivation of Cannabis for Medicinal Purposes (Annex 2).

i.Regulations should be developed to provide for the governance structure, security measures, cultivation requirements, processing requirements, packaging and labelling, testing and research regulation requirements, research implementation arrangements, transportation requirements, community engagement, compliance to international standards.

4.Due to the sensitive nature of Cannabis, and in compliance with the UN Single Convention on Narcotic Drugs (1961), Article 28, MOH should put in place a system of control in collaboration with other relevant Ministries, such as Ministry of Agriculture.

5.A Multi-Stakeholder Technical Committee on Medical Cannabis for Scientific Use should be constituted under the leadership of the National Health Research Authority (NHRA) to spearhead the implementation process.

Key Definitions

Cannabis refers to 'the flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by tops) from which the resin has not been extracted, by whatever name they may be designated' [3].

Cannabis is a generic term plant genus with various ways of classifications in literature. However, for the sake of this Policy Brief we will divide Cannabis into two as defined by the Colorado (USA) Constitution [4]:

- Marijuana being a plant of the genus Cannabis and any part of that plant, whether growing or not, with a concentration of delta-9-tatrahydrocannabinol (THC) of more than 0.3%
- Industrial Hemp being any Cannabis with a concentration of THC no more than 0.3%.

Cannabinoids are chemical compounds that act on cannabinoid receptors (CB1) in cells that alter neurotransmitter release in the nervous system [5].

Phytocannabinoids are cannabinoids that occur naturally in the cannabis plant. Cannabis acts through these chemical substances. There are two phytocannabinoids of importance for this Policy Brief: Delta-9-tatrahydrocannabinol (THC) and Cannabidiol (CBD). THC is the psychoactive substance in Cannabis and is responsible for the pleasurable subjective effects [6].

Cannabidiol (CBD) is similar in structure to THC but has no psychoactive effects [7].

Medicinal Cannabis or Cannabis for medical use refers to the use of cannabis and its constituents, natural or synthetic, to treat disease or alleviate symptoms under professional supervision [8].

Medical purposes: 'A medicine (medicinal substance; that is, whether synthetic and/or natural, pure or in the form of a preparation) is a substance used, designed or approved for the following medical purposes: a) Improving health and well-being; b) Preventing and treating disease (including the alleviation of symptoms of that disease); c) Acting as a diagnostic aid; d) Aiding conception or providing contraception; e) Providing general anaesthesia' [8].

Scientific purposes: 'The designation of the use of a drug for "scientific purposes" is appropriate when it is used as a tool for investigating mechanisms of health or disease or when investigating the use of a product as a medicine. In patients, the investigation would be done as part of a clinical trial, which requires prior approval from the research ethics committee' [8].
Feasibility of Policy Options – The likelihood that the policy option will be adopted and implemented.

Low Feasibility: No or small likelihood of being adopted and implemented
Medium Feasibility: Medium likelihood of being adopted and implemented
High Feasibility: High likelihood of being adopted and implemented.

TECHNICAL DOSSIER

Background

Global Legal Perspective on Medicinal Cannabis

Cannabis for medicinal and scientific use is governed by three United Nations Conventions: Single Convention on Narcotic Drugs (1961 as amended by the 1972 Protocol), Convention on Psychotropic Substances (1971), and Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988). (Annexe 3). The International Narcotics Control Board (INCB) is the independent and quasi-judicial monitoring body for the implementation of the United Nations international drug control conventions. It was established in 1968 in accordance with the Single Convention on Narcotic Drugs (1961)[

https://www.incb.org/incb/en/about/mandate-functions.html
].

A number of countries have legalized Cannabis for medical use. As at March 29, 2019, these include Australia, Argentina, Bermuda, Canada, Chile, Colombia, Croatia, Cyprus, Czech Republic, Denmark, Finland, Germany, Georgia, Greece, Israel, Italy, Jamaica, Lesotho, Luxembourg, Malta, North Macedonia, Norway, Netherlands, New Zealand, Peru, Poland, San Marino, South Africa, Sri Lanka, Switzerland, Thailand, United Kingdom, Uruguay, Vanuatu, Zimbabwe. In the United States of America, 33 States plus the District of Columbia, have legalized Cannabis for medical use, but Federally, Cannabis remains illegal for any use [1,2].

Zambian Legal Perspectives on Medicinal Cannabis

In Zambia, the cultivation and use of Cannabis and other related substances is mainly regulated by the following laws:
1.The Dangerous Drugs Act, Chapter 95 of the Laws of Zambia, 1967 (Annex 4)
2.Narcotics and Psychotropic Substances Act, Chapter 96 of the Laws of Zambia, 1993 (Annex 5)
3.The Medicines and Allied Substances Act of 2013 (Annex 6)
The Dangerous Drugs Act of 1967 under the Ministry of Health provides for the control of the importation, exportation, production, possession, sale, distribution and use of dangerous drugs; and to provide for matters incidental thereto. The Act applies to raw opium, coca leaves, poppy-straw, cannabis, cannabis resin and all preparations of which cannabis resin forms the base. Any person who wants to import or export any of the above products needs a license issued by the Minister of Health. The Narcotics and Psychotropic Substances Act of 1993 under the Ministry of Home Affairs, prohibits or criminalizes the trafficking, importation, exportation, possession and cultivation, use of, manufacture, and trading in narcotics, including cannabis.

The Medicines and Allied Professions Act of 2013 provides for the general regulation of the pharmaceutical industry in Zambia under the Zambia Medicines Regulatory Authority (ZAMRA). Anyone who wants to cultivate cannabis for medicinal or scientific purposes is expected to apply to ZAMRA, the authority designated to enforce and administer the provisions of this Act.

Problem Statement

In spite of the legal provision to allow for cultivation and dealing with cannabis for medicinal and scientific purposes, that provision has never been implemented in Zambia. The main reason for non-implementation of the law in this regard is the fact that there are no regulations to operationalize the legal provisions. Regulations have not been developed possibly due to lack of evidence on the medical value of implementing a program for medicinal cannabis in Zambia. In the recent past, the Ministry of Health has been under pressure to issue licenses to prospective developers to cultivate Cannabis for medicinal and/or scientific purposes. This evidence brief aims to answer specific questions to provide evidence for the Ministry of Health to make an informed decision. The main questions are:
What evidence is there on the effectiveness and safety of medicinal cannabis in treating various medical conditions? And how strong and reliable is the evidence on the efficacy and effectiveness of cannabis for medicinal use? Is there justification for Zambia to grow Cannabis for medicinal use? What evidence is there on the effectiveness and safety of medicinal cannabis in treating various medical conditions? And how strong and reliable is the evidence on the efficacy and effectiveness of cannabis for medicinal use? Is there justification for Zambia to grow Cannabis for

medicinal use?

The Research Evidence on Medical Cannabis

Introduction

Our review of systematic reviews published between January 2014 and February 2019, shows a long list of medical conditions treated with medical cannabis. The grade of quality and weight of this evidence in terms of effectiveness to treat a particular condition is mixed.
This brief relies on evidence graded as high to moderate quality on the GRADE quality system [9] and graded as moderate to conclusive weight, based on the grading by the Health and Medicine Division, formally the Institute of Medicine (IOM) of the National Academies, USA [10]. The GRADE is a system used to assess the quality of evidence of each outcome in a systematic review against eight criteria (including risk of bias, indirectness, inconsistency, imprecision, publication bias). The quality of evidence for each outcome is graded as High, Moderate, Low, or Very Low (Table 1). The assessment reflects the degree of confidence in the effect estimate (e.g. Odds ratio, Risk Ratio). A rating of High means that having assessed all potential problems with the quality of the evidence, we are so confident in our estimate that further research is very unlikely to alter that effect estimate.

We constructed table 2 to explain the rating of evidence into Conclusive, Substantial, Moderate, Limited or Insufficient as used by the National Academies of Sciences, Engineering, and Medicine [10]. Any reference to 'conclusive' or non-conclusive evidence in this evidence brief has the meaning and interpretation as explained in table 2.

We reviewed systematic reviews, umbrella reviews, and controlled clinical trials on the efficacy, effectiveness, and safety of cannabis for medicinal use in chronic pain, treatment of nausea and vomiting associated with chemotherapy, Epilepsy, and Schizophrenia/Psychosis. The main focus will be on pain as that is the area that medicinal cannabis has been most used for. This evidence brief will also review and synthesize evidence on Hemp for medicinal/therapeutic and health use, considering that it has less or no psychoactive effects.

Table 1 The GRADE Rating System

Quality Rating	Meaning
High	We are **very confident** that the true effect lies close to the estimated effect size.
Moderate	We are **moderately confident** that the true effect likely to be close to the estimated effect size, but there is a possibility that it is substantially different.
Low	Our confidence in the effect is **limited** because the true effect may be substantially different from the estimated effect size.
Very Low	We have **very little confidence** in the effect estimate because the true effect is likely to be substantially different.

Adapted from Ryan R. Hill (2016):
https://cc.cochrane.org/sites/cc.cochrane.org/files/public/uploads/how_to_grade.pdf
Based on the GRADE Handbook found at:
https://gdt.gradepro.org/app/handbook/handbook.html#h.9rdbelsnu4iy

Table 2 Weight of Evidence

Weight of Evidence	Meaning and description	Interpretation
Conclusive evidence	There is **strong evidence** from Randomized Controlled Trials (RCTs) to support the conclusion that the medicine is effective or ineffective to treat the health endpoint of interest (e.g. pain, vomiting, etc).	The interpretation of this level of evidence is that there are a lot of supportive findings from good quality studies with no credible opposing findings. Therefore a **firm conclusion** can be made and the **limitations to the evidence such as chance, bias, and confounding can be ruled out with reasonable confidence.**
Substantial Evidence	There is **strong evidence** to support the conclusion that the medicine is effective or ineffective to treat the health endpoint of interest.	The interpretation is that there are several supportive findings from good quality studies with very few or no credible opposing findings. Therefore a **firm conclusion** can be made, but **minor limitations** such as chance, bias, and confounding cannot be ruled out with reasonable confidence.
Moderate Evidence	There is **some evidence** to support the conclusion that the medicine is effective or ineffective to treat the health endpoint of interest.	There are several supportive findings from good to fair quality studies with very few or no credible opposing findings. Therefore a general conclusion can be made, but **limitations** such as chance, bias, and confounding cannot be ruled out with reasonable confidence.
Limited Evidence	There is **weak evidence** to support the conclusion that the medicine is effective or ineffective to treat the health endpoint of interest.	There are supportive findings from to fair quality studies or mixed findings with most favouring one conclusion. Therefore a conclusion can be made, but there is **significant uncertainty** due to chance, bias, and confounding.
No Evidence or Insufficient Evidence	There is **no or insufficient evidence** to support the conclusion that the medicine is effective or ineffective to treat the health endpoint of interest.	There are mixed findings, a single poor quality study, or health endpoint has not been studied at all. Therefore no conclusion can be made because there is **substantial uncertainty** due to chance, bias, and confounding.

Table constructed based on information from National Academies of Sciences, Engineering, and Medicine (2017). The health effects of cannabis and cannabinoids: The current state of the evidence and recommendations for research. Washington, DC: The National Academies Press.
http://nap.edu/24625

Effect of medical cannabis on Chronic Pain

There is moderate quality evidence that medical cannabis alleviates chronic pain, especially neuropathic pain; however, the weight and quality of the evidence is still mixed. The current evidence is therefore not conclusive.

Is medical cannabis effective for reduction of chronic pain?
The National Academies of Sciences, Engineering, and Medicine concludes in the National Academies Press that there is conclusive or substantial evidence that cannabinoids are effective for treatment of chronic pain in adults [11]. This conclusion is mainly based on a systematic review by Whiting PF et al [10]. In a systematic review and meta-analysis of 28 randomized clinical trials (RCTs) and based on the GRADE approach to assess the quality of the RCTs, Whiting and others in 2015 concluded that there

was moderate quality evidence to support the use of Cannabinoids for the treatment of chronic pain [12]. Cannabinoids were associated with short term adverse events. Although this was a rigorously conducted review, Whiting and his team point out a number of methodological issues in the studies they reviewed. Caution should therefore be exercised in relying on just this evidence synthesis as conclusive or substantial evidence. It is also important to take into account other evidence and counter-evidence in the literature to have a balanced view. Below, we summarize other evidence on the subject matter. In 2015, Andreae and others in a systematic review with Bayesian meta-analysis of 5 RCTs and 178 participants concluded that inhaled cannabis may provide short-term relief for one in 5 to 6 patients with neuropathic pain [13]. The authors however caution that the small number of studies and participants, the short follow-up, shortcomings in allocation concealment, and considerable attrition limit the conclusions that can be made from their review [13].

Shannon M. Nugent and others in a systematic review of 27 RCTs, 2 systematic reviews, and 3 observational studies in 2017 report that limited evidence suggests that Cannabis may alleviate neuropathic pain in some patients, but there is insufficient evidence for other types of chronic pain. Limited evidence suggests that Cannabis is associated with an increased risk of adverse mental health effects [14].

According to Peter Reynolds, there is a large quantity of good quality evidence that demonstrate efficacy and safety in treating chronic pain, especially neuropathic pain [15]. He substantiated this conclusion by referring to five sources [16, 17, 18, 19, 20]. Please note that this was not a systematic review study and Reynolds did not apply any quality standard to assess and grade these studies. Below, we summarize the studies quoted by Reynolds: In 2007, Abrams DI and others in a placebo-controlled RCT of 50 patients with painful HIV-associated sensory neuropathy reported that smoked cannabis reduced daily pain by 34% versus 17% in the placebo group (p=0.03) [16].

Wilsey B et al. in the same year (2007) in a double-blind placebo-controlled cross over trial of 38 patients with chronic pain using 3.5% and 7% delta-9-THC smoked cannabis concluded that cannabis may be effective at ameliorating neuropathic pain. [17] They observed significant analgesia expressed as a 0.0035 reduction in visual analog scale (VAS) pain intensity per minute from both the 3.5% and the 7% cannabis compared to placebo. The combined group of 3.5% and 7% versus placebo produced a difference of -0.0035 (95% CI: -0063 to -0.0007; P=0.016).

A phase 2 double-blind placebo-controlled crossover clinical trial of 28 HIV positive patients with neuropathic pain by Ellis and others using smoked cannabis of 1 to 8% delta-9-TCH reported greater pain relief with cannabis than placebo: Median difference in the descriptor differential scale (DDS) pain intensity change of 3.3 points, effect size 0.60; p=0.016. The proportion of patients achieving at least 30% pain relief with cannabis was 0.46 (95% CI: 0.28 to 0.65) compared to 0.18 (95% CI: 0.03 to 0.32) in the placebo group. [18]

A randomized controlled trial of 23 adults with post-traumatic or post-surgical neuropathic pain found that the average pain intensity using an 11-point numeric rating scale (0=no pain, 11=worst pain) was significantly lower on 9.4% delta THC (pain intensity rate=5.4) than on 0% delta THC (6.1)(P=0.023; difference=0.7, 95% CI: 0.02-1.4)[19].

The last study that Peter Reynolds quoted was a randomized, placebo-controlled, double-dummy, double-blind trial that compared the magnitude and duration of analgesic effects of smoked marijuana and dronabinol under well controlled conditions using a validated experimental model. In this study where pain response was assessed using the cold-pressor test (CPT) in 30 healthy daily marijuana smokers, Cooper and others report that under controlled conditions marijuana and dronabinol decreased pain, with dronabinol producing longer-lasting decreases in pain sensitivity and lower ratings of abuse-related subjective effects than marijuana [20].

However, a recent (2018) Cochrane systematic review concludes as follows: "The potential benefits of cannabis based medicine (herbal cannabis, plant derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms. The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities from the studies, together with their small sample sizes" [21]. And the plain language summary states, "there is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain."

As we conclude this section on medicinal cannabis and chronic pain, we need to answer a critical policy relevant question: Is medical cannabis more effective and better tolerated than other currently available analgesics for chronic pain?

We found no evidence from systematic reviews or RCTs showing that medical cannabis is more effective and better tolerated than opiates or other analgesics. There is some conflicting ungraded evidence that cannabis use may reduce opiate use in patients with chronic pain.

A retrospective cross-sectional survey of 244 medical cannabis patients with chronic pain found that medical cannabis was associated with a 64% decrease in opioid use (n=118), decreased number and side effects of medications, and an improved quality of life (45%) [22]. However, other evidence shows that marijuana use, especially chronic use, may affect pain response to injury by requiring greater use of opioid analgesia [23].

Effect of medical cannabis on nausea and vomiting due to chemotherapy

Is medical cannabis effective in reducing nausea and vomiting associated with cancer chemotherapy?

There is moderate quality evidence that medical cannabis is effective in reducing nausea and vomiting associated with cancer chemotherapy. The current evidence may not be regarded as conclusive or substantial, despite the fact that there are cannabis-based medications already licensed for use in this condition.

According to Whiting and others (2015), there was low-quality evidence suggesting

that Cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy [12]. In a review of three trials, Whiting found that compared to placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% versus 20%; OR 3.82, 95% CI: 1.55 to 9.42). Based on this and other evidence, the National Academies of Sciences, Engineering, and Medicine, writing in the National Academies Press (2017) reported that there was conclusive or substantial evidence that cannabis or cannabinoids are effective as antiemetics in the treatment of chemotherapy-induced nausea and vomiting [10]. The Academies review team appears to have based their conclusion on the reviews by Whiting et al (2015) and Smith et al (2015) [24]. The team however acknowledged the fact that despite some positive findings in favour of Cannabinoids, Smith and team concluded that there was no evidence to support the use of cannabinoids over current first-line antiemetics and that cannabinoids should be considered as adjunctive treatment for people that are on moderately or highly emetogenic to chemotherapy that are refractory to other antiemetics, when all other options have been tried.

The Academies of Sciences, Engineering and Medicine review team also refer to three cannabinoid-based drugs, Dronabinol (Marinol ®), Nabilone (Cesamet ®) and Syndros® the liquid formulation of Dronabinol; all licensed by the US Food and Drugs Administration (FDA) and indicated for nausea and vomiting due to cancer chemotherapy. Considering Whiting's conclusion and the caution by Smith and others, we advise to exercise caution and conclude that there is moderate evidence to support a conclusion that cannabinoids are effective for cancer therapy related nausea and vomiting.

Effect of medical cannabis in Schizophrenia

Current evidence on the efficacy and effectiveness of medicinal cannabis in treating Schizophrenia is Limited.

Is medicinal cannabis effective and safe in the treatment of Schizophrenia?
In a recently published (2019) systematic review of literature on Cannabis and mental illness, Lowe Darby and other concluded that current evidence supports more harmful effects of recreational cannabis use on mental illness rather than therapeutic [25].

Effect of medical cannabis in Multiple Sclerosis

Is medicinal cannabis effective and safe in the treatment of Multiple Sclerosis?

Current evidence on the efficacy and effectiveness of medicinal cannabis in treating spasticity associated with multiple sclerosis is moderate.

The National Academies of Sciences, Engineering, and Medicine (2017) reported that there was conclusive or substantial evidence that cannabis or oral cannabinoids are effective for improving patient-reported multiple-sclerosis spasticity symptoms; but there is limited evidence that cannabis or oral cannabinoids are effective in improving physician-measured multiple sclerosis spasticity symptoms [10]. They also report that there is moderate evidence that cannabis or cannabinoids (primarily nabiximols) are effective in improving short-term sleep outcomes in individuals with sleep disturbance associated with multiple sclerosis. The Academies team based their conclusions on the effect of cannabis or cannabinoids on multiple sclerosis spasticity on two systematic reviews by Whiting et al (2015) and Koppel et al (2014) [26] and one placebo-controlled crossover clinical trial by Leocani et al. [27]. Whiting et al. concluded that there was moderate evidence to support the use of cannabinoids for spasticity. Based on five trials, Whiting and team report an average reduction in the Ashworth spasticity scale[The Ashworth spasticity scales assesses the effect of anti-spasticity drugs on spasticity in multiple sclerosis. https://www.sralab.org/rehabilitation-measures/ashworth-scale-modified-ashworth-scale] (Weighted Mean Difference, -0.12; 95% CI: -0.24 to 0.01).

Barbara S. Koppel and others, in a systematic review of medical marijuana of 34 studies, with 8 rated Class 1 based on American Academy of Neurology classification scheme for therapeutic articles (Class 1 being most rigorous and 4 as least rigorous)[https://www.aan.com/siteassets/home-page/policy-and-guidelines/guidelines/about-guidelines/17guidelineprocman_pg.pdf

], concluded that with regard to spasticity, oral cannabis extract (OCE) is effective (based on 2 Class 1 studies); nabiximols and THC are probably effective for reducing patient centred measures; it is possible both OCE and THC are effective for reducing both patient centred and objective measures at one year. They warn however that the risks and benefits of medical marijuana should be weighed carefully. They found that the risks of serious adverse psychopathologic effects was nearly 1%. They also conclude that comparative effectiveness of medical marijuana versus other therapies is unknown for the indications studied (which included spasticity in multiple sclerosis).

Effectiveness, efficacy, and safety of Hemp as medicine and health product

Effectiveness, efficacy, and safety of Hemp as medicine

Literature suggests that cannabidiol (CBD) has broad therapeutic value [28]. According to Jamie Corroon and Joy A. Phillips, CBD products are currently purchased online, over the counter and at cannabis-specific dispensaries throughout most of the US despite the fact that CBD is generally deemed a Schedule 1 controlled substance by the US Drug Enforcement Administration and renounced as a dietary supplement ingredient by the US Food and Drugs Administration [28].
The question is how strong and conclusive is the current evidence on the effectiveness and safety of CBD in treating specific medical conditions to warrant licensing?

CBD and Epilepsy

To-date, there is only one CBD product, Epidiolex, recently licensed (June, 2018) by the Food and Drug Administration (FDA) in the USA. Epidiolex (Cannabidiol oral solution) was launched in November, 2018 and is used for the treatment of seizures associated with the Lennox-Gastaut Syndrome (LGS) or Drovet syndrome.

There are at least two key pieces of recent evidence supporting the above use:

a)In a randomized placebo-controlled clinical trial, Devinsky and others report that among 120 children with Dravet syndrome from 23 Centers in the US and Europe, the median frequency of convulsive seizures per month decreased from 12.4 to 5.9 in the CBD group compared with a decrease from 14.9 to 14.1 in the placebo (P=0.01); the percentage of patients who had at least a 50% reduction in convulsive seizure frequency was 43% with CBD and 27% with placebo (OR=2, 95% CI=0.93 to 4.30, P= 0.08); the frequency of seizures of all types significantly reduced with CBD (P= 0.03) but there was no reduction in nonconvulsive seizures; 5% of patients became seizure free with CBD and none in the placebo (P=0.08). Adverse events occurred more frequently in the CBD group than placebo; these included diarrhoea, vomiting, fatigue, pyrexia, somnolence, abnormal liver function tests. [29]
b)In a randomized placebo-controlled clinical trial of 225 patients with Lennox-Gastaut Syndrome (LGS) aged 2-55 years from 30 clinical centres in the US and Europe, Devinsky and others report that the median percentage reduction in drop-seizure frequency from baseline 41.9% in the 76 patients taking 20mg CBD, 37.2% in patients taking 10mg CBD, and 17.2% in the placebo group (P=0.005 for the 20mg CBD versus placebo and P=0.002 for the 10mg versus placebo). The most common adverse events among patients in the CBD group were somnolence, decreased appetite, and diarrhea and occurred more frequently in the 20mg CBD group. Six patients in the 20mg CBD group and one patient in the 10mg CBD group discontinued the trial medication because of adverse events and were withdrawn from the study. Nine percent (n=14) who received CBD had elevated liver aminotransferase concentrations. [30].
Other than in various combinations with THC, there is currently no conclusive evidence that CBD is effective in any other medical condition.

CBD in Schizophrenia

Current evidence on the effectiveness of CBD on Schizophrenia is mixed and not conclusive.

From several references, Darby J.E. Lowe and others present studies that show that CBD is effective in treating Schizophrenia as well as studies that show that it is not effective [22]. McGuire and others in an exploratory double-blind parallel-group trial of 88 patients with Schizophrenia, report that after 6 weeks of treatment, patients on CBD had lower levels of positive psychotic symptoms (PANNS: Treatment difference = -1.4, 95% CI: -2.5, -0.2) and were more likely to have been rated by the treating physician as improved (CGI-I: Treatment difference = -0.5. 95% CI: -0.8, -0.1) compared to Placebo. CBD was well tolerated, and the rates of adverse events were similar between the CBD and placebo groups [31].

FM Leweke and others in a therapeutic exploratory (phase 2) double-blind, parallel-group randomized controlled clinical trial of 42 patients with Schizophrenia or schizophreniform psychosis comparing CBD versus amisulpride, report that either treatment was safe and led to significant clinical improvement; CBD displayed a better side effect profile [32]. However, Boggs and colleagues, in a randomized, placebo-controlled, parallel group, fixed-dose study of oral CBD (600mg/day) or placebo augmentation in 36 stable antipsychotic-treated patients diagnosed with schizophrenia, found that CBD augmentation was not associated with an improvement in the Matrics Consensus Cognitive Battery (MCCB) or Positive and Negative Syndrome Scale (PANSS) scores; though overall, CBD was well tolerated with no worsening of mood, suicidality, or movement side effects [33].

CBD in chronic pain

There is currently no conclusive evidence on the effectiveness of CBD on its own (i.e. not in combination with THC) in alleviating chronic pain, despite its use by patients for that purpose. The majority of the studies on cannabinoids and chronic pain have focused on chronic neuropathic pain and specifically on nabiximols (Sativex), which is a combination of THC and CBD rather than CBD alone [34].

In a cross-sectional study of 2,409 CBD users by Jamie Corroon and others, 62% of users reported using it to treat a medical condition; top on the list being chronic pain, arthritis/joint pain, and anxiety [24]. In this study, 35.8% of those who used CBD to treat a medical condition (N=1483) said CBD treated their medical condition(s) "very well by itself." But the effect on pain was not specifically assessed.

CBD in the treatment of nausea and vomiting associated with chemotherapy

There is no conclusive high-quality evidence on the efficacy of CBD in treating nausea and vomiting related to cancer chemotherapy.

There is evidence that cannabinoids, THC and CBD combined, may alleviate nausea and vomiting associated with cancer chemotherapy, but even such evidence is not conclusive. Whiting, in a systematic review based on three studies, reported that compared to placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% versus 20%, OR 3.82, 95% ci: 1.55-9.42). However, he concludes that there was low quality evidence suggesting that cannabinoids were associated with the improvements in nausea and vomiting due to chemotherapy. Cannabinoids were associated with an increased risk of short-term adverse events [12].

Donald I. Abrahams, in a recent review article in the European Journal of Medicine, the National Academies of Sciences, Engineering and Medicine states that the committee on health effects of cannabis and cannabinoids concluded that there was conclusive or substantial evidence that Cannabis or Cannabinoids are effective for treatment of pain in adults, chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis [10]. This claim has however been questioned by Campbell and colleagues recently who carefully analysed the evidence used in coming up with this conclusion and the limitations of such evidence [34].

Health Benefits of Hemp

We were not able to obtain any RCTs or systematic reviews on the health benefits of hemp in the literature search. However, there is a lot written about the health benefits of hemp; mainly focused on nutrition. Hempseed contains approximately 30% oil and

25% protein, with a considerable amount of dietary fibre, vitamins and minerals [35]. Hempseed oil contains over 80% polyunsaturated fatty acids and is exceptionally rich in two of the essential fatty acids- linoleic acid (omega-6) and alpha-linolenic acid (omega-3). The two main proteins in hempseed are edestin and albumin. Other literature shows that 49% of hempseed contain edible oil that contains 76% essential fatty acids [36]. There are apparently a lot of food products derived from hempseed; these include oil, flour, milk, bakery products, chocolate, beer, etc. [37].

The evidence on the efficacy, effectiveness and safety of medicinal cannabis in various combinations of THC and CBD is mixed. Combinations of THC and CBD have been shown to have medicinal value for alleviating chronic pain of nerve origin, nausea and vomiting associated with cancer chemotherapy, certain types of epilepsy, and some mental illness (schizophrenia). However, although there are some cannabis-based medicines licensed in the United States, overall, the current research evidence is not fully conclusive on the effectiveness and safety of the THC/CBD combinations.

There is greater potential for the use of CBD-based cannabis medicines because they have fewer side effects and CBD has essentially no psychoactive effects; with no potential for abuse. There is also potential for use of industrial hemp (containing CBD) for other health benefits, especially in food and nutrition.

Cultivation of medicinal cannabis for scientific purposes only

1.The overarching recommendation is for Zambia to implement a program for cultivation of medicinal cannabis for scientific purposes only.

2.The specific recommendation is that the Minister of Health may issue licenses for cultivation of Industrial Hemp (Cannabidiol with no more than 0.2% THC) for scientific purposes only until such a time that there is conclusive evidence to warrant cultivation on a wider scale for medical use.

3.The current legal framework should be supported by subsidiary legislation that will provide the manner and form of the licensing process as recommended by the Committee on cultivation of Cannabis for Medicinal Purposes (Annex 2).

i.Regulations should be developed to provide for the governance structure, security measures, cultivation requirements, processing requirements, packaging and labelling, testing and research regulation requirements, research implementation arrangements, transportation requirements, community engagement, compliance to international standards.

4.Due to the sensitive nature of Cannabis, and in compliance with the UN Single Convention on Narcotic Drugs (1961), Article 28, MOH should put in place a system of control in collaboration with other relevant Ministries, such as Ministry of Agriculture.

5.A Multi-Stakeholder Technical Committee on Medical Cannabis for Scientific Use should be constituted under the leadership of the National Health Research Authority (NHRA) to spearhead the implementation process.

Conclusion

Recommendations

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