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Background

Medical cannabis refers to the use of whole, unprocessed marijuana plant or its basic extracts as medical therapy to treat disease or alleviate symptoms. It is a plant-based medicine from the *Cannabis sativa* or *Cannabis indica* species that contain the active compounds or psychoactive cannabinoids called tetrahydrocannabinol or delta-9-tetrahydrocannabinol or commonly known as THC. Cannabinoids can be administered orally, sublingually, or topically; they can be smoked, inhaled, mixed with food, or made into tea. They can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of cannabidiol (CBD), or manufactured synthetically. Currently, the two main cannabinoids from the marijuana plant of interest for medical treatment are THC and CBD.

The potential medicinal properties of cannabis and its components have been the subject of research and heated debate for decades among health care professionals. Evidences have examined the efficacy and safety of cannabis for the treatment of a variety of conditions including chronic pain (non-cancer and cancer pain, neuropathic pain, multiple sclerosis related, rheumatoid arthritis, musculoskeletal and chemotherapy-induced pain), nausea and vomiting (palliative care patients, cancer patients, chemotherapy patients), spasticity associated with multiple sclerosis or paraplegia, sleep disturbance, loss of appetite and weight loss associated with HIV/ AIDS, psychiatric, movement and neurodegenerative disorders (Alzheimer's disease, anorexia nervosa, anxiety, dementia, dystonia, schizophrenia, Huntington's disease, Parkinson's disease, post-traumatic stress disorder, psychosis and Tourette syndrome), epilepsy, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and glaucoma. Although findings suggested that cannabinoids may have role in the management of those conditions, the extent of its safety and effectiveness remain uncertain. Hence, there is a need to review the current evidence across the range of indications to provide evidence-based recommendation on their therapeutic potential.

Policy question

Should medical cannabis be used in Malaysia?

Objective

To assess the effectiveness and safety of medical cannabis to treat disease or alleviate symptoms.

Methods

Literature search was developed by the main author and *Information Specialist* who searched for published articles pertaining to cannabis for medical use. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® ALL 1946 to August 30, 2022. Parallel searches were run in PubMed, US FDA and INAHTA database. Search was limited to articles in English and in human. Detailed search strategy is as in Appendix 3. The last search was performed on 2nd September 2022. Additional articles were identified from reviewing the references of retrieved articles.

Results:

Overview of included studies

A total of 10,460 records were identified through electronic databases searching via Ovid interface while five were identified from other

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sources (references of retrieved articles). Following the removal of 9,539 duplicates, 926 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 182 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 182 full text articles, 47 full text articles were included. The 47 full text articles which were finally selected in this review comprised of 38 systematic review and meta-analysis (psychiatric [5], pain [10], neurodegenerative [3], epilepsy [4], multiple sclerosis [5], substance abuse [2], gastrointestinal [2], obstetrics and gynaecology [2], and others [5]) one RCT (eye), and eight economic evaluation studies (multiple sclerosis [7] and epilepsy [1]).

Results of clinical effectiveness review

1. Chronic pain

Ten studies evaluated medical cannabis for the treatment of chronic pain. The conditions causing the chronic pain varied between studies and included mostly neuropathic pain, chronic cancer-related pain, non-cancer pain, and diabetic peripheral neuropathies. Overall, there was some evidence that medical cannabis may reduce pain but less evidence for an effect on other outcomes such as quality of life (QoL) and global impression of change. Studies generally suggested that non-inhaled medical cannabis or cannabinoids may results in a non-clinically significant improvement in pain relief, physical functioning, and sleep quality compared with placebo. However, the potential benefits of cannabis-based medicine might be outweighed by their potential harm due to an increased risk of short-term adverse events (AEs).

2. Epilepsy

Five studies evaluated medical cannabis for the treatment of epilepsy. Most of the population were patients with Dravet or Lennox-Gastaut Syndrome, and drug resistant epilepsy syndrome. Overall, there was high certainty evidence that showed highly purified CBD (Epidiolex or Epidyolex) was effective as an adjunct treatment for drug resistant seizure in patients with Dravet syndrome and Lennox-Gastaut syndrome. There was moderate to high certainty evidence for the efficacy of Epidiolex or Epidyolex to be used as an adjunct in the treatment for other drug resistant seizure in both adult and children. Similarly, there was low to moderate certainty evidence that showed cannabinoid oil effective as an adjunct treatment for drug resistant seizure in both adult and children.

3. Multiple sclerosis

Five studies evaluated the benefit and harms of cannabinoids for reducing symptoms in adults with multiple sclerosis. Overall, there was moderate certainty evidence that showed Nabiximols (Sativex®) was effective as an adjunct treatment for moderate to severe spasticity in patients with multiple sclerosis. However, there was low certainty evidence on effectiveness of other form of cannabis and cannabis-based medicine as adjunct treatment for moderate to severe spasticity in patients with multiple sclerosis. The evidence also suggested that Sativex® has an acceptable safety profile.

4. Neurogenerative and neurodevelopmental disorder

Three studies evaluated the effects of various types of medical cannabis on cognitive functioning and neurodevelopment function. Overall, low-to-moderate quality evidence showed acute effects of cannabis use on neurocognitive function. Cannabis intoxication led to deficits (small to moderate) in numerous cognitive domains, most notably executive functions, verbal learning and memory, and processing speed. Residual effects have been documented suggesting that the detrimental effects of cannabis persist beyond the period of acute intake. Meanwhile, there were limited evidence regarding the impact of comorbid cannabis uses in vulnerable groups such as adolescents and young adults with attention deficit and hyperactive disorder (ADHD).

5. Eye disorder

Only one study investigated whether single oral administration of dronabinol (a synthetic THC) altered optic nerve head blood flow (ONHBF) and its regulation. The proof of concept of dronabinol (orally administered, low-dose) showed short-acting increases in ONHBF without affecting the intra ocular pressure or inducing psychoactive side effects.

6. Psychiatric disorder and substance abuse

Five studies evaluated the effects of medical cannabis as a treatment to improve symptoms among patients with psychiatric disorder while two studies on substance abuse. Overall, there was low quality evidence for the use of medical cannabis in the treatment of generalised anxiety disorder, post-traumatic stress disorder (PTSD), and management of cannabis withdrawal. There was inadequate evidence to support the use of medical cannabis for the management of substance use disorder, particularly cannabis use disorder.

7. Obstetrics and gynaecology disorder

Two studies evaluated the effects of medical cannabis for the treatment of gynaecological pains. Findings in general indicated that cannabis improved pain from numerous gynaecologic conditions including chronic pelvic pain, vulvodynia, endometriosis, and gynaecologic malignancy. However, interpretation of the studies is limited due to varying cannabis formulations, delivery methods, and dosages that preclude a definitive statement about cannabis for gynaecologic pain relief. In the same way, women using marijuana during their pregnancies were at significantly increased risk of adverse neonatal outcomes.

8. Gastrointestinal tract disorder

Two studies were included for assessment of medical cannabis use in inflammatory bowel disease (IBD) and functional dyspepsia. Overall, there was moderate to high certainty that cannabis and cannabinoids showed significant improvement in QoL in IBD with improvement of gastrointestinal symptoms while reduced length of hospital stay and risk of parenteral nutrition. However, cannabis and cannabinoids did not induce clinical remission, affect inflammatory parameters, prevent relapse, and reduce IBD related complications. On the other hand,

there was limited evidence to suggest that cannabis and cannabinoids may alleviate symptoms of functional dyspepsia and upper gastrointestinal symptoms associated with delayed gastric emptying.

9. Chemotherapy-induced nausea and vomiting

Two studies evaluated medical cannabis for the treatment of nausea and vomiting in adults and children undergoing chemotherapy. Overall, there was low evidence to shows cannabis and cannabinoids were effective in reducing the symptoms of chemotherapy induced nausea and vomiting. Most of this evidence compared cannabis and cannabinoids with placebo or older generation of antiemetics.

10. Fibromyalgia

One systematic review evaluated the efficacy, tolerability, and safety of cannabinoids for fibromyalgia symptoms in adults. Overall, there were no significant differences between nabilone and placebo noted for fatigue and depression. Outcome on disability was not reported. However, nabilone had better effects on sleep than amitriptyline. Moreover, there were no significant differences between the two drugs for pain and health related QoL (HRQoL). There were no reported data for the Fibromyalgia Impact Questionnaire (FIQ) subscales of anxiety, disability, fatigue and depression. The evidence showed no significant differences between the two drugs in the Profile of Mood States.

11. Human Immunodeficiency Virus/ AIDS infection

One systematic review evaluated medical cannabis as a treatment for appetite stimulation in patients with HIV/ AIDS-associated anorexia. However, the reviewer showed no significant difference in weight gain in patients receiving dronabinol compared to placebo.

12. Insomnia

One systematic review evaluated the effect of medical cannabis for the treatment of insomnia disorder. Overall, there was low evidence on effectiveness of nabilone in treating insomnia, particularly on both Pittsburgh Sleep Quality Questionnaire (PSQI) and Insomnia Severity Index (ISI) score. The evidence showed that there was no difference between nabilone and amitriptyline in overall sleep quality as measured by the Leeds Sleep Evaluation Questionnaire (LSEQ) but that nabilone resulted in with amitriptyline.

Safety

With regard to adverse health effects associated with the use of medical cannabis, most finding indicated that there was a significantly greater risk of any AE, serious AE, withdrawals due to AE, gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders, psychiatric disorders, renal and urinary disorders, asthenia, balance problems, confusion, diarrhoea, disorientation, drowsiness, dry mouth, euphoria, fatigue, hallucination, nausea, somnolence, and vomiting. Other AEs did not show significant differences between groups.

Economic implication

Seven economic evaluations on the use of cannabinoids as treatment for multiple sclerosis and one on epilepsy were included in the review.

All of the evaluations were conducted from the Western healthcare perspectives, and none were conducted from Asian healthcare perspectives. Findings revealed that Sativex® was likely to be cost-effective compared to current standard of care for the treatment of spasticity due to multiple sclerosis in Germany, Spain, Wales, Italy and Belgium. However, based on willingness-to-pay (WTP) threshold of £30,000 per QALY gained in the UK, Sativex® appears unlikely to be considered cost-effective. For epilepsy, adjunctive cannabinoid oil compared to clobazam/ valproate alone may be a cost-effective treatment for Dravet syndrome from the perspective of Canadian health care system.

Conclusion

Based on systematic review of effectiveness and safety of medical cannabis in various disease populations, a total of 47 studies (38 systematic review, one RCTs, and eight economic evaluation studies) of moderate-quality were included. Findings in general indicated that cannabinoids as compared to either placebo or existing treatment showed statistically significant beneficial effects for the treatment of chronic neuropathic pain, epilepsy (Dravet Syndrome, Lennox-Gastaut Syndrome, and drug resistant seizure), spasticity due to multiple sclerosis or paraplegia, psychiatric (anxiety and movement disorders due to Tourette syndrome), gynaecologic conditions (pelvic pain, cramping, muscle spasms, endometriosis, primary dysmenorrhea, interstitial cystitis, and bladder pain syndrome), gastrointestinal tract disorder (inflammatory bowel disease), fibromyalgia, and insomnia. However, these results should be taken with caution due to heterogeneity of the included studies, with some potential risk of bias. There were uncertainty or inconclusive evidence on whether cannabinoids can be used for the treatment of neurogenerative disorder (dementia) and neurodevelopmental (ADHD), substance use disorder (cannabis use disorder), gastrointestinal tract disorder (functional dyspepsia and upper gastrointestinal symptoms, irritable bowel syndrome, and ulcerative colitis), nausea and vomiting due to chemotherapy, and appetite and weight gain in HIV/ AIDS. Furthermore, cannabinoids were not significantly different for the treatment of cancer pain, sleep disturbance, depression, schizophrenia, Crohn' disease, and glaucoma. However, cannabinoids were associated with an increased risk of short-term AEs.

Recommendation:

Based on the above review, there was limited evidence available on the effectiveness and safety of cannabis for medical use. These are the recommendations on their therapeutic potential for these disorders based on synthesis of the retrieved evidences:

1. Chronic pain:

a. Non-cancer pain

The current available evidence is inadequate for the committee to recommend the use of medical cannabis for chronic pain in clinical use.

b. Cancer-pain

The currently available evidence is inadequate for the committee to recommend the use of medical cannabis in cancer pain. Well-designed RCTs are recommended to evaluate the use of medical cannabis in cancer pain.

2. Epilepsy

The current available evidence is supportive for the committee to recommend the use of Epidiolex and cannabinoid oil as an adjunct treatment for drug resistant seizure in patients with Dravet syndrome, Lennox-Gastaut syndrome and other drug resistant seizure in both adult and children with monitoring on the potential adverse events.

3. Multiple sclerosis

The current available evidence is supportive for the committee to recommend the need for well-designed clinical trials to further ascertain the effectiveness, safety, acceptance and clinical need of Sativex® for its use in the treatment of moderate to severe spasticity in multiple sclerosis 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.

4. Neurogenerative disorder and neurodevelopmental

The current available evidence is inadequate for the committee to recommend the use of medicinal cannabis products as treatment for neurodegenerative, to either improve cognition or behavioural component of dementia. There is a need for well-designed clinical trials to examine the efficacy, safety, and acceptance and clinical need of cannabis and cannabis-based medicine for the treatment of cognition or behavioural component of dementia. In the same way, cannabis and cannabis-based medicine should not be recommended to be used in neurodevelopmental conditions including ADHD until further safety evidence is available.

5. Eye disorder

The current available evidence is inadequate for the committee to recommend the use of medical cannabis in any eye conditions (glaucoma).

6. Psychiatric disorder and substance abuse

The current available evidence is inadequate for the committee to recommend the use of medical cannabis for the treatment of psychiatric and substance use disorder.

7. Obstetrics and gynaecology disorder

The current available evidence is supportive for the committee to recommend further studies and evaluation on medical cannabis for gynaecological pain. Pregnant women should be counsel regarding the risks of in utero exposure and encouraged to abstain from use in pregnancy and while breastfeeding.

8. Gastrointestinal tract disorder:

a. Inflammatory bowel disease (IBD)

The current available evidence is supportive for the committee to recommend the use of medicinal cannabis products for IBD patients to reduce gastrointestinal symptoms, improve QoL, and reduce length of hospital stay. There is insufficient evidence to support the use of medicinal cannabis products as a disease modifying medication in IBD. Larger and more uniform studies are needed to add robustness of evidence on effectiveness of cannabis and cannabinoids.

b. Functional dyspepsia

The current available evidence is inadequate for the committee to recommend the use of medicinal cannabis products for functional dyspepsia and upper gastrointestinal symptoms associated with delayed gastric emptying. Further studies are needed to explore the efficacy and safety of medical cannabis in patients with epigastric pain syndrome or patients with upper gastrointestinal symptoms associated with delayed gastric emptying.

9. Chemotherapy-induced nausea and vomiting

The current available evidence is inadequate for the committee to recommend the usage of medical cannabis in patients with chemotherapy induced nausea and vomiting. Further studies are needed to explore the efficacy and safety of medical cannabis against the standard of care in patients with chemotherapy induced nausea and vomiting.

10. Fibromyalgia

The current available evidence is inadequate for the committee to recommend the usage of medical cannabis in patients with fibromyalgia. Further good quality studies are needed to explore the efficacy and safety of medical cannabis in treating fibromyalgia.

11. HIV/ AIDS infection

The current available evidence is inadequate for the committee to recommend the usage of medical cannabis in patients with anorexia in HIV/ AIDS. Further good quality studies are needed to explore the efficacy and safety of medical cannabis in treating anorexia in HIV/ AIDS.

12. Insomnia

The current available evidence is inadequate for the committee to recommend the usage of medical cannabis in patients with insomnia. More convincing evidence are needed to show the efficacy and safety of medical cannabis in treating insomnia.