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THE MEDICINAL USE OF CANNABINOIDS: A REVIEW OF THE CURRENT LITERATURE

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ABSTRACT

Introduction: The medicinal use of cannabinoids is increasing in the United States, despite controversies over its efficacy and safety. Therefore, clinicians will encounter patients who desire or elect to use cannabinoids and should be able to advise them on cannabis-related clinical issues based on the current evidence. This article reviews the main areas of clinical cannabinoid use, discusses the quality and consistency of the evidence for these areas, and examines cannabinoid side effects.

Methodology: The literature search for this review was carried out to identify papers published between 1995 and 2016 in in the following electronic databases: PubMed, and Cochrane Review. Several combinations of the following keywords were used: "Cannabinoids" OR "marijuana" AND "pain", fibromyalgia", "multiple sclerosis", "huntingtons", "treatment", "cancer", "dementia", "nausea", "vomiting", "hepatitis", "HIV", "schizophrenia", and "inflammatory bowel disease. The quality and consistency of the studies selected was evaluated according to the Strength of Recommendation Taxonomy (SORT) and key recommendations with each main clinical indication.

Results: Cannabinoids do appear effective for multiple conditions including spasticity and neuropathic pain related to MS, fibromyalgia, chronic pain, and cancer-associated nausea and vomiting, there are significant side-effects related to their use.

Conclusion: Despite efficacy, cannabinoids are best reserved for use as a second-line treatment, due to the multiple common side effects, withdrawal symptoms, and addiction potential.

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INTRODUCTION

The medicinal use of cannabionoids is increasing in the United States, despite controversies over its efficacy and safety. Therefore, clinicians will encounter patients who desire or elect to use cannabinoids and should be able to advise them on cannabis-related clinical issues based on the current evidence. This article reviews the main areas of clinical cannabinoid use, discusses the quality and consistency of the evidence for these areas, and examines cannabinoid side effects. Studies on cannabionids are limited by lack of preparation uniformity and different preparations may have different effects on clinical conditions. The *Cannabis*plant, contains more than 60 cannabinoids, although the primary psychoactive cannabinoid is delta-9-tetrahydrocannabinol (THC). Cannabinoids preparations include herbal cannabis, synthetics such as dronabinol and nabilone, cannabis extracts and formulations, nabiximols, cannabis-derived oromucosal spray, and oral cannabis extract. Herbal cannabinoids are compounds of *Cannabis sativa* and *Cannabis indica*plant and include delta-9-tetrahydrocannabinol (THC) and cannabidiol. Synthetic cannabinoids are extracts and congeners of THC and cannabidiol produced in the laboratory. "Medical marijuana" may refer to either herbal cannabinoids or both herbal and synthetic cannabinoids.

MATERIALS AND METHODS

The literature search for this review was carried out to identify papers published between 1995 and 2016 in in the following

electronic databases: PubMed, and Cochrane Review. Several combinations of the following keywords were used: "Cannabinoids" OR "marijuana" AND "pain", fibromyalgia", "multiple sclerosis", "huntingtons", "treatment", "cancer", "dementia", "nausea", "vomiting", "hepatitis", "HIV", "schizophrenia", and "inflammatory bowel disease." The selection process for the articles used in this review was based on the both the aim of the study and the quality of the evidence. The quality and consistency of the studies selected was evaluated according to the Strength of Recommendation Taxonomy (SORT) and key recommendations with each main clinical indication (Ebell, 2004). The level of evidence for the main clinical indications was assessed using three levels of evidence as defined below:

Level 1 Evidence: is represented by the most valid reports with patient-oriented outcomes and includes randomized trials and systematic reviews of randomized controlled trials. Both the RCTs and systematic reviews must have only very small flaws in design, analysis, follow-up, or bias.

Level 2 Evidence: is represented by reports addressing patient-oriented outcomes, but not meeting the quality criteria to achieve Level 1 evidence labeling. Examples include randomized trials with significant flaws in design, analysis, follow-up, or bias.

***Level 3 Evidence*e:** presents reports that are not based on analysis of patient-oriented outcomes. Examples include case series, case reports, expert opinion, and conclusions extrapolated indirectly from scientific studies.

Treatment of Clinical Conditions with Cannabinoids

Table 1. Conditions for which Cannabinoids may be useful in treatment

Condition	Strength of Recommendation	Best Level of Evidence
Treatment of muscle spasticity and non-neuropathic pain in Multiple Sclerosis	Level A (for oral cannabis extract) Level B (for THC and nabiximols)	Level 2
Chronic pain (non-neuropathic, and non-cancer related)	A	Level 2
Fibromyalgia	B	Level 2
Chorea associated with Huntington's Disease (short term use)	C	Level 3
Cancer associated Nausea and Vomiting	B	Level 3

Multiple sclerosis (MS)

Based on RTCs with some limitations, cannabinoids appear to improve muscle spasticity, pain, sleep, and spasms in patients with MS and affects appear sustained at 12 months (Corey-Bloom, 2012; Flachenecker, 2014; Wade *et al*., 2010; Wade *et al*., 2003; Zajicek *et al*., 2005 and Zajicek, 2012). The American Academy of Neurology recommendations for multiple sclerosis note that oral cannabis extract (OCE) or delta-9 tetrahydrocannabinol (THC) or oromucosal cannabinoid spray (nabiximols) may be offered to reduce patient-reported symptoms of spasticity and pain, except for neuropathic pain (Yadav, 2014). Although cannabinoids may improve central neuropathic pain in patients with MS, the use for this condition has less evidence and is associated with adverse effects including dizziness, nausea, and feeling intoxicated in up to 92% of patients (Rog, 2005 and Langford, 2013). Cannabinoids may also be useful in the treatment of urinary symptoms in MS patients. In a RCT of 135 subjects, the addition of cannabis-derived oromucosal spray to the current treatment regimen improved urinary symptoms (urgency, nocturia, frequency) in patients with MS but did not reduction in daily episodes of incontinence (Kavia, 2010). Despite the improvements in muscle symptoms, pain, and urinary symptoms discussed above, there is little evidence that cannabis products slow progression in adults with progressive MS (Zajicek, 2013).

Chronic Pain

A 2015 systematic review concluded that cannabinoids that there is moderate quality evidence to support the use of cannabinoids in the treatment of chronic pain (Whiting, 2015). The European Federation of Neurological Societies (EFNS) recommends cannabinoids as a pharmacologic treatment option with efficacy for managing multi-etiology neuropathic pain (EFNS Level A) (Attal, 2010). The use of cannabinoids for chronic neuropathic or cancer pain, however, has questionable efficacy and side-effect risk may outweigh any benefit(Ware, 2010; Lynch, 2011; Wilsey, 2013; Selvarajah, 2010; van den Beuken-van Everdingen, 2006).

Chemotherapy-induced nausea and vomiting

The use of medical marijuana for refractory nausea and emesis in patients with a cancer is controversial. Based on a Cochrane review, cannabinoids may be useful for treating refractory chemotherapy-induced nausea and vomiting (Smith, 2015). However, methodological limitations of the RCTs included in the review limited conclusions and noted further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify the conclusions (Smith, 2015). A 2015 systematic review from JAMA noted there was low-quality evidence suggesting that cannabinoids are associated with improvements in nausea and vomiting due to chemotherapy. Cannabinoids were also associated with an increased risk of short-term adverse events including dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination (Whiting, 2015). The American Society of Clinical Oncology (ASCO) recommends cannabinoids be reserved for patients intolerant or refractory to 5HT3 receptor antagonists, NK-1 receptor antagonists, and dexamethasone (American Society of Clinical Oncology1, 2006).

Fibromyalgia

Based on a small randomized crossover trial without intention-to-treat analysis, nabilone may improve sleep quality compared to amitriptyline in patients with fibromyalgia and chronic insomnia (level 2 [mid-level] evidence). However, compared to amitriptyline, nabilone was associated with more frequent adverse effects including dizziness, nausea, and dry mouth (Ware, 2010). The Canadian Fibromyalgia Guidelines Committee recommends considering a trial of prescribed pharmacologic cannabinoid in patients with fibromyalgia, especially in patients with important sleep (Mary-Ann Fitzcharles, 2012). Based on a small randomized trial of 40 patients, nabilone may also improve pain and anxiety in patients with fibromyalgia (Skrabek, 2008).

Other possible Clinical Indications

In a 2015 review, there was low-quality evidence to support the use of cannabinoids for the treatment of sleep disorders, and Tourette syndrome (Whiting, 2013).

Rheumatoid arthritis

Based on a small randomized trial of 58 patients, cannabis-derived oromucosal spray may reduce pain and improve disease activity in patients with rheumatoid arthritis (Blake, 2006).

Spinal cord injury

Nabilone may reduce spasticity in patients with spinal cord injury, based on a small randomized crossover trial with 12 subjects (Pooyania, 2010).

Cancer-associated anorexia and weight loss

There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapyin a 2015 systematic review (Whiting, 2015). However, cannaboids do not appear to increase appetite and appears less effective than megestrol acetate for weight gain and increasing appetite in patients with cancer-associated anorexia (Cannabis-In-Cachexia-Study-Group, 2006 and Jatoi, 2002).

Posttraumatic stress disorder

Two separate case series reported that cannabinoids appeared to reduce PTSD symptoms (Greer, 2014 and Fraser, 2009).

Inflammatory bowel disease

Self-medication rates with cannabinoid for IBD range from 14%-21%, based on a cross-sectional study of 100 patients with ulcerative colitis and 191 patients with Crohn's disease attending a tertiary care clinic. Cannabis was used to relieve inflammatory bowel disease-related symptoms (abdominal pain, diarrhea, reduced appetite) in 14% of patients with ulcerative colitis and 21% of patients with Crohn's disease (Lal, 2011). There is a paucity of large studies of cannabinoids for IBD, but based on a small randomized trial, cannabanoids may reduce symptom severity and appears to increase remission in patients with refractory Crohn's disease (Naftali *et al*., 2013).

Cannabinoids have Conflicting, Insufficient, or Lack of Efficacy for:

- Cancer pain (van den Beuken-van Everdingen *et al*., 2016)
- Hepatitis C infection (Costiniuk, 2008; Ishida, 2008; Hézode, 2005; Marcia Russell, 2014 and Sylvestre, 2006).
- Huntington disease (Curtis *et al*., 2009 and Armstrong, 2012).
- Parkinson disease (Carroll, 2004).
- Epilepsy (Gloss, 2014)
- Schizophrenia (McLoughlin, 2014).
- Alzheimer disease or dementia (Krishnan *et al*., 2009; van den Elsen *et al*., 2015; Shelef, 2016).
- Use in HIV Treatment for appetite, anorexia, and HIV-associated anorexia (Attal *et al*., 2010; Beal, 1995 Haney, 2005 and Lutge, 2013).

Side Effects : Dependency and withdrawal are concerns with cannabinoids, although common side effects of cannabinoids include dizziness (most common), amnesia, drowsiness, depression or euphoria, disorientation, and ataxia (Lutge *et al*., 2015 and Tongtong Wang, 2008). Chronic smoking of cannabinoids can lead to an increase in symptoms of cough, phlegm, and wheezing, appetite changes, tachycardia, palpitations, gynecomastia, decreased testosterone, and decreased sperm motility (Tashkin, 2012; Fronczak, 2012; Bowman, 2012). Cannabinoids also appear to impair driving and are associated with an increased risk of motor vehicle collision based on a systematic review (Hall, 2010). In adolescents, cannabinoid use also appears to increase the risk of subsequent psychosis later in life (Moore *et al*., 2007). Chronic cannabinoid use can also cause a hyperemesis syndrome with nausea, vomiting, and abdominal pain (Simonetto, 2012). An acute abstinence from cannabinoids may lead to cannabis withdrawal symptoms includinganxiety or nervousness, depressed mood, decreased appetite or weight loss, restlessness, headaches, abdominal pain, shakiness/ tremors, sweating, fever, chills, insomnia, irritability, anger, or aggression (Gorelick, 2012). Based on the currrent available literature, cannabinoids should be discontinued during pregnancy. Maternal use of cannabis during pregnancy associated with reduced fetal size during pregnancy and at birth, risk for preterm birth, spontaneous birth, and small-for-gestational-age birth, stillbirth, and decreased IQ (El Marroun *et al*., 2009; Saurel-Cubizolles, 2014; Varner *et al*., 2014 and Goldschmidt *et al*., 2008).

Conclusion

Although cannabinoids do appear effective for multiple conditions including spasticity and neuropathic pain related to MS, fibromyalgia, chronic pain, and cancer-associated nausea and vomiting, there are significant side-effects related to their use. Cannabinoids are best reserved for use as a second-line treatment, due to the multiple common side effects, withdrawal symptoms, and addiction potential.

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