Sapporo Medical Journal
Volume 54, Issue 07, July, 2020

The Use of Medical Cannabis as an Effective Form of Treatment: The Benefits in Epilepsy Disorder and the Potential Drawback in Chronic Non-Cancer Pain

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Abstract— In recent years, there has been an increasing interest in the use of medical cannabis and its importance in medical treatment. Particularly, this issue of using medical cannabis has received considerable critical attention in epilepsy disorder and chronic non-cancer pain. The purpose of this paper is to review recent research to determine the effect of medical cannabis as a form of medication. It suggests that there is a positive relationship between the use of medical cannabis and the reduction in the number of seizure frequency for those who suffer from epilepsy diseases. The paper also discusses the other argument evidencing that medical cannabis has a negative effect on those with chronic non-cancer pain. Finally, it concludes that medical cannabis is useful for the treatment of epilepsy diseases. At the same time, there should also be continued efforts to make the decision about using medical cannabis more accessible for medical purposes. A major recommendation in this paper is to continue conducting further research and to have support from the government in order to consolidate this finding.

Keyword: Medical cannabis, Epilepsy disorder ,Chronic non-cancer pain.

Introduction:
The controversy about scientific evidence for cannabis has raged unabated for over a century. Cannabis derives from Indian hemp plants, including cannabis sativa, and is also known as marijuana (Saxena 2016). The cannabis plant contains more than 500 components, with only around 100 of cannabinoids having been recognized. The two significant chemicals used in the medical field include Tetrahydrocannabinol (psychoactive cannabis) and Cannabidiol (non-psychoactive cannabis) (Genevieve et al. 2017). While Cannabidiol does not affect the brain function, Tetrahydrocannabinol produces a chemical substance that may change the brain function (ibid). Also, cannabis oil is obtained from a crude plant of cannabinoids concentration (ibid).

In recent years, there has been an exponential growth in terms of exploring the therapeutic potential of cannabis in particular epilepsy and control the chronic non-cancer pain. Epilepsy can be defined as a chronic disease of the brain that can lead to a change in neuronal networks (neurological system) and is characterized by sudden recurrent episodes of convulsion and loss of consciousness because of atypical electrical activity in the brain (Fisher et al. 2014). Chronic pain is the most common complaint when seeking medical advice in primary care, and it is defined as pain that lasts more than twelve weeks (Gureje et al. 1999). While the number of epilepsy attacks is on the increase, reaching about 65 million patients worldwide (Hesdorffer et al. 2013), evidence about the effectiveness of medical cannabis for epilepsy and chronic non-cancer pain remains limited (Hauser et al. 1993). Besides personal interest, the main reason for choosing this topic is the identification of some entirely interesting evidence.

This paper aims to critically argue for the use of cannabis as a medication in order to determine whether or not it can be an effective solution in terms of reducing the seizure frequency and other chronic non-cancer pain. It will be suggested that medical cannabis has a negative effect on those with the chronic non-cancer pain. This paper will be argued that there is a positive relationship between the use of medical cannabis and the reduction in the number of seizure frequency for those who suffer from epilepsy diseases. There is a great deal of research recommending more future studies with robust findings and evidence to strengthen this argument. After providing a brief background with some historical data about

cannabis, this paper will then move on to the discussion part which will analyses some of the evidence to identify if medical cannabis can be used effectively in the treatment of epilepsy diseases and chronic non-cancer pain. Finally, it will conclude and provide recommendations on how effective the use of cannabis for medical purposes can be.

Materials and Methods:
For this review, we used a variety of sources to search through PubMed, Embase, Scopus. The search was performed by using combinations of the following key words and or their equivalents: 'Medical cannabis', Marijuana, Cannabidiol', Epilepsy disorder', Seizure, Chronic non-cancer pain'. Manuscripts published in English as full-text articles, and or as abstract were included in the study. Unfortunately, the search conference procedures and manuscripts published in other languages were not specifically handed out.

1. Background:

In recent years, much attention has been drawn to the use of cannabis as a treatment for many diseases. However, there has been a controversy surrounding health benefits or risks, medical implications, ethical considerations, the legality of such use and also safety (Bridgeman and Abazia 2017).

The cannabis plant was first used in China around 4.000 years B.C and the medical use of cannabis began about 1000 years B.C in India, with the plant being used as an analgesic and anticonvulsant (Zuardi 2006). Halfway through the 19th century, the cannabis was effectively in use in the west by Doctor William B. O'Shaughnessy. In America, the first clinical conference regarding cannabis was held in 1860 (ibid). In the second half of the 19th century, there was a growing body of published articles in Europe and the United States about the use of cannabis for medical purposes (ibid). At that time, the medical research reports used some cannabis for the treatment of pain and nausea (Lankenau, Kioumarsi and Reed 2017). After that, there was a restriction on cannabis use and sale in 1937, followed by removal from the market as a prescription in 1942. In 1970, governments started considering cannabis as an illegal substance and put in place various controls on its use (Bridgeman and Abazia 2017). As such, there appears to be a lack of knowledge or little research with regards to cannabis (ibid).

Moreover, California was the first state to allow the use of cannabis for medical purposes under the physician's supervision (ibid). Also, on the 1st of January 2017, 28 states introduced cannabis as a medical treatment (ibid). Since 1996, there has been a motivation towards the use of cannabis for therapeutic purposes, as in pain, seizure, nausea and psychological problems (Lankenau, Kioumarsi and Reed 2017). However, there appear to be some concerns about the potential effects of using cannabis as a medical treatment.

In recent years, there has been so much interest in the use of cannabis in the treatment of some medical conditions, such as the ones already mentioned. A number of researchers have expressed their concerns regarding the impact of cannabis on some medical conditions, as in its use with acquired immune deficiency syndrome (AIDS) patients, improving the appetite of those using chemotherapy treatment and decreasing eye pressure in the case of glaucoma (McCarthy 2010). In fact, this year there has been a big debate in the UK regarding one patient who used cannabis oil as a treatment to control the seizure attacks. This patient was prescribed it by the physician from Canada. However, the home officers in the airport confiscated the cannabis oil because the health authorities in the UK do not still approve cannabis as a medication (Busby 2018). This led to a widespread debate to identify the benefits and how to achieve full access to cannabis as a treatment in the UK and also how to control any related adverse effects. It should also be pointed out that cannabis is still a federal issue from a legal, ethical and safety point of view (McCarthy 2010). Therefore, medical cannabis is a controversial topic, and its use can be challenging, which require for specific official guidelines or protocols for legalising the use of this substance as a medication.

2. Discussion: The effectiveness of cannabis as a treatment

2.1 Chronic non-cancer pain:

At present, some medical researchers are increasingly focusing their efforts on finding out about the effectiveness of medicinal cannabis in the treatment of chronic pain (Häuser et al. 2018). In this respect, some studies have generally reported the positive impact that medical cannabis has in terms of reducing chronic non-cancer pain. On the other hand, some studies state that medical cannabis is not effective in minimizing chronic non-cancer pain. Taking into account that each of those research efforts have definite merits and faults, this section of the paper will argue that there is an irrelevant effect of medical cannabis in reducing chronic non-cancer pain. The different recent studies will be analyzed to explore whether or not medical cannabis is effective in reducing chronic non-cancer pain.

A recent systematic review and meta-analysis study the advantages and risks of therapeutic cannabinoids in the treatment of chronic, non-cancer pain. Johal et al. (2020)concludes that there has been moderate evidence to support cannabinoids in 2-week treatment of chronic non-cancer pain. Similar findings have been found at later times, but the confidence in impact is low. There is no evidence that cannabinoids raise the risk of serious adverse effects, while non-serious adverse reactions can be frequent in the short term after use (ibid).

Numerous recent studies have argued that there is an inverse relationship between the use of medical cannabis and the control of chronic non-cancer pain. Campbell et al. (2018) reported some negative effects due to cannabis use with chronic non-cancer pain. For example, there has been an increase in pain severity. Also, some participants experienced a decrease in pain by using the self-efficacy questionnaire. In addition, the severity of anxiety scores increased in the majority of participants. This observational cohort study, which included 1514 patients, assessed the use of cannabis in terms of treating chronic non-cancer pain, by adding to opiates to control the pain (ibid). This study took over four years of follow-up, including interviews, phone call interviews or a self-complete questionnaire (ibid). The authors included some statistical analyses to discover any relationship between using cannabis and pain control to strengthen the validity of the results. In addition, the authors took into account the pain scales and lifestyle quality, such as social involvement, ability to work, and sleep patterns. However, this study has some flaws in methodology. For example, the data collection is subjective as it is based on patient self-opinion, which can lead to doubts about the study reliability. As such, the number of participants and the duration of the study can be considered as some of the strongest points. Also, the authors considered using the triangulation approach (interviews, self-report and participant observations) to achieve validity and reliability.

In the same vein, Stockings et al. (2018) in their recent systemic review and meta-analysis concluded that medical cannabis has an irrelevant effect on controlling chronic non-cancer pain. Also, there were no statistical relation effects in the quality of life (no improvement in sleep patterns and patient emotional impression). This type of study, which involved 47 randomized controlled trials and 57 observational studies with a total of 9958 participants, is considered the best method to evaluate the efficacy and to also minimize bias. However, the main weakness of this study lies in that some observational studies included a small number of patients while others considered medical cannabis alongside other painkiller medications. The number of studies is considered one of the key factors to overcome the limitation. This view is supported by Allende-Salazar and Rada (2017) who conducted a recent systemic review and concluded that there was an inconspicuous effect of medical cannabis in terms of reducing the chronic non-cancer pain. The researchers explained that low quality might contribute to the negative effects of medical cannabis. In addition, the authors determined that there is a significant increase in the rates of adverse effects on patients using medical cannabis.

Similarly, Wilson et al. (2018) claimed that there is no relationship between cannabis use and the treatment of chronic non-cancer pain. This cross-sectional study involved 150 patients who completed a

questionnaire covering the use of cannabis, pain score, depression, anxiety and self-efficacy of pain experiences. In addition, Feingold et al. (2016) stated that 10% to 20% of participants who use cannabis-based medicines might experience the increased risk of depression and anxiety. Overall, the side effects outweigh the benefits in this situation.

However, many researchers have found that medical cannabis can have a positive effect in the treatment of chronic non-cancer pain. Lynch and Campbell (2011) conducted a systemic review of randomized control trials to assess the effectiveness of cannabinoids in relieving pain. This study involved eighteen trials published between 2003 and 2010, with a total of 766 participants. The quality of the studies was excellent, with 6.1 out of 7 according to the Oxford scale. This study found a positive statistic correlation between the use of cannabinoids and pain severity, along with an improvement in the quality of life, in particular, sleep. The participants' pain intensity decreased from severe to moderate, with no huge difference in the painkiller medication (ibid). Although the studies were excellent in quality, the most critical weakness can be ascribed to the fact that it used a small sample size, while the short duration may affect the validity of the review, leading to the overestimation of the study results.

Another systematic review was carried out by the National Academies of Science, Engineering and Medicine (2017) to consider the effectiveness and safety of cannabis. The authors indicated that there is a positive effect when treating a case of chronic pain with the help of cannabis, in particular with neuropathic pain (pain affecting the nervous system). Even though this review included several low-quality studies in terms of methodology, it reinforced the findings of Hoggart et al. (2014) and Haroutounian et al. (2016) who identified that there is a relationship between cannabis and decrease in the severity of pain. Equally, two other studies (Häuser, Petzke and Fitzcharles 2017; Moulin et al. 2014) went as far as to suggest that cannabis can be resorted to as a third line treatment in the case of neuropathic pain. Overall, despite the presence of some flaws in methodology; namely the small sample size and the short duration of the studies that may compromise the reliability of the studies, the majority of studies were more optimistic about cannabinoids' analgesic effect and role in reducing the pain.

Collectively, it could be that the researcher is overestimating the effect of cannabis in reducing chronic non-cancer pain. Moreover, the recent evidence fails to identify if there is an impact of the use of medical cannabis in terms of reducing chronic non-cancer pain, with some studies suggesting the opposite; i.e. increased depression and anxiety. Therefore, it is essential to conduct more research to strengthen these findings, minimize the limitations and improve the reliability and validity.

2.2 Epilepsy disorder:

Hitherto, there has been a rapid increase in the number of studies over the last decade investigating how medical cannabis can help manage or relieve some diseases, such as epilepsy disorder. Various epileptic patients have difficulty in controlling intractable and refractory seizure, which could lead to social segregation, low marriage rates, unemployment, psychological problems and affect their quality of life (Wahab 2010). There has been considerable controversy about whether medical cannabis can be effective in reducing seizure attacks and improving the quality of life. This section will argue that there is an effect for using medical cannabis in terms of reducing epileptic attacks. The different recent studies will be reviewed to analyse the effect of medical cannabis.

Many studies suggest there is a positive relationship between the treatment of epilepsy disorders and use of medical cannabis. Both Thiele et al. (2018) and Devinsky et al. (2017) used the same method, which is the randomized, double-blind placebo-controlled trial with a 14-week duration, to explore the efficacy of medical cannabis. The latter was added to the antiepileptic therapy in patients suffering from a resistant severe complex form of epilepsy (Devinsky et al. 2017 and Thiele et al. 2018). Taken together, the authors' results suggested that there is approximately a 50% reduction on seizure attacks with the use of medical cannabis. Also, the most striking finding to emerge from the data is that there is a considerable improvement in the quality of life (ibid). Although there were also some minor adverse effects in patients

who received cannabidiol, including drowsiness, diarrhea, fatigue and change in appetite (ibid), the randomized, double-blind, placebo-controlled trial applied to those studies can be considered as a golden standard for epidemiologic studies, thus increasing the strength of the studies.

Encouragingly, these figures are consistent with those found by Tzadok et al. (2016) who found that 66 out of 74 participants reported a reduction in epilepsy attacks, as a result of using cannabidiol and tetrahydrocannabinol by dissolving them in olive oil for intractable resistant epilepsy (ibid). Furthermore, the authors noted an improvement in behavior, alertness, language, communication skills, sleep and motor skills. However, there were some adverse effects, including somnolence (sleepiness), fatigue, gastrointestinal problems, which led to the withdrawal of some patients from the study (ibid). This type of study could be the reason for those side effects; however, the cohort longitudinal studies have some advantages, such as the long duration of the period and the number of participants sampled, which might lead to selection bias from the lack of control groups.

In the pooled analysis, the most recent systemic review of control and observational evidence included six randomized controlled studies; two of which were discussed above (Thiele et al. 2018 and Devinsky et al. 2017) and 30 observational studies (Stockings et al. 2018). The authors concluded that there is a positive correlation regarding the reduction in seizure frequency when patients used medical cannabis once they have mixed it with the antiepileptic medication (ibid). Nevertheless, they reported minor adverse effects with the use of medical cannabis (ibid). This type of research integrates best practice, best evidence and includes a large number of participants. However, in Stockings et al. review (2018), the fact that the majority of studies analyzed were observational studies and used self-report data may raise the chance of bias.

A more recent systematic review and meta-analysis has been conducted to evaluate cannabidiol and medicinal cannabis beneficial and adverse effects for treatment-resistant epilepsy (de Carvalho Reis et al. 2020). This study showed that CBD treatment for epilepsy is effective in reducing the incidence of seizures (ibid). Adverse events were more predominant in short-term compared to long-term CBD treatment that suggesting lower adverse reaction profiles during long-term treatment (ibid). Further studies using medicinal cannabis are required to validate profiles of adverse effects for prolonged treatment period, and research on formulations with low levels of Δ9-tetrahydrocanabidiol are also needed to enable the comparison of weight loss with other adverse effects linked to CBD or cannabis (ibid). This study has some limitations in relation to the descriptive analysis pertain to eleven open studies, which are likely to involve bias in the results.

A more recent observational study has been conducted to assess the effectiveness of medical cannabis in the treatment of refractory epilepsy by applying cannabis oil (cannabidiol and tetrahydrocannabinol) to 56 patients (Hausman-Kedem et al. 2018). The study concluded that there was a decrease in the mean monthly seizure attacks by around 50%, which is similar to the results of other studies conducted by Devinsky et al. (2016) and Tzadok et al. (2016) (ibid). There were also other positive outcomes among patients, such as improvement in sleep patterns, help in being more alert and better communication skills, which supports the findings of Hussain et al. (2015) and Tzadok et al. (2016). Similarly, this was comparable in terms of the percentage of adverse effects to two other studies; namely Devinsky et al. (2016) and Tzadok et al. (2016). The most common side effect is somnolence, with rates ranging from around 46 to 79% (Hausman-Kedem et al. 2018). Also, one of the greatest strengths of the study is the in-depth information given about cannabis oil. Nonetheless, the sample size is an issue to be considered.

However, many researchers have shown no strong correlation between reduction in seizure frequency and utilizing medical cannabis. Gloss and Vickey (2014) conducted a systemic review of randomized control trials to assess the effectiveness of medical cannabis in reducing seizure attacks. The authors included four studies which may be considered low quality regarding their methodology and because of the small sample size (49 participants). The review concluded that there was insufficient data to confirm the

effectiveness of cannabidiol in reducing the seizure attacks (ibid). In the same vein, Koppel et al. (2014) published a systemic review, which arrived at the same conclusion in that there is still no current data reliable enough to support or reinforce the effectiveness of using medical cannabis in decreasing the frequency of seizure. Therefore it seems that the previous two systematic reviews could not support their position due to some validity issue.

However, although the two systemic reviews conducted by Koppel et al. (2014) and Gloss and Vickey (2014) provided valid conclusions, there are some flaws and limitations, including the small number of participants and the short duration of the research in the majority of studies. Also, in the review provided by the authors, there is low-quality evidence, and some of the studies have no control groups. The studies depended upon the relatives' reports to determine the number of seizure attacks. Thus, it is evident that there is a possibility of selection bias, while the validly of studies is also questionable.

Based on the discussion above, it appears that medical cannabis is strongly associated with a decrease in the number of seizure attacks. Although the collected evidence shows that there are some minor adverse effects, medical cannabis has proven its effectiveness for helping treat patients. However, it is essential to continue conducting more double-blind, randomized studies with longer timeframes and larger sample sizes to reinforce the existing findings and limit the reported side effects. There is continual hope to reduce the occurrence of seizure attacks in order to achieve optimum results and full cure.

Conclusion :

The most apparent finding to emerge from this study is that medical cannabis can be useful in the treatment of epilepsy disorder. However, this paper has also established that medical cannabis may have irrelevant effects in relation to chronic non-cancer pain. This controversy paper aimed to determine the effectiveness of medical cannabis as a medical treatment.

One of the most significant findings to emerge from this study is that using medical cannabis contributes to the reduction of up to 50% of seizure attacks in patients suffering from a resistant severe complex form of epilepsy. This result opens up whole horizons and gives new hope to achieve the full care for patients suffering from moderate to milder types of epilepsy disorder. Nevertheless, it was difficult to make predictions about the effect of such use in chronic non-cancer pain cases. It appears that using medical cannabis is effective in epilepsy instances, while there has been no evidence to support such a positive impact in the case of chronic non-cancer pain .

The generalizability of these results is subject to certain limitations. For instance, the small number of participants, the short period of study and the risk of overestimating the effects may affect the validity, reliability and accuracy of the study. Moreover, further research could also be conducted to strengthen the effect of medical cannabis and to limit the flaws in the methodology adopted. Likewise, continued efforts are needed to make the necessary decisions about using the medical cannabis more accessible for medical purposes. Furthermore, more government support and encouragement should be made available to ensure a suitable environment for randomized, double-blind research with a more significant number of participants and longer timeframes in order to meet the validity, reliability and accuracy requirements of this type of research. It is only recently (03 August 2018) that the UK government has recognized the medical benefits of cannabis and the recommendations to consider prescription (Godlee 2018). This result may lead to further research opportunities to ascertain the medical uses of cannabis.

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