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PART 1: PICO WORKSHEET (1200 words)

Evidence-based practice of pain management

You are to use the design a question using the PICO framework to examine the topic above. For example with A nurse-led topic you may choose to explore if heart failure nurse-led clinics impact on the quality of life in patients with heart failure. Please be sure that you complete ALL sections of the PICO framework document.

PICO Worksheet and Search Strategy

Brief description of the problem or situation (50 words):

Chronic pain is a serious health condition usually affecting adults. In Australia, one in five adults suffers from chronic pain. Opioid painkillers (the usual medication given) are seen to be less effective in many cases. Medical cannabis can be a treatment alternative as it has both analgesic and anti-inflammatory properties.

P	Population	Adults with Chronic Pain
I	Intervention	Medical cannabis
C	Control/comparison	No-treatment
O	Outcomes	Treatment, pain reduction

Write out your question:

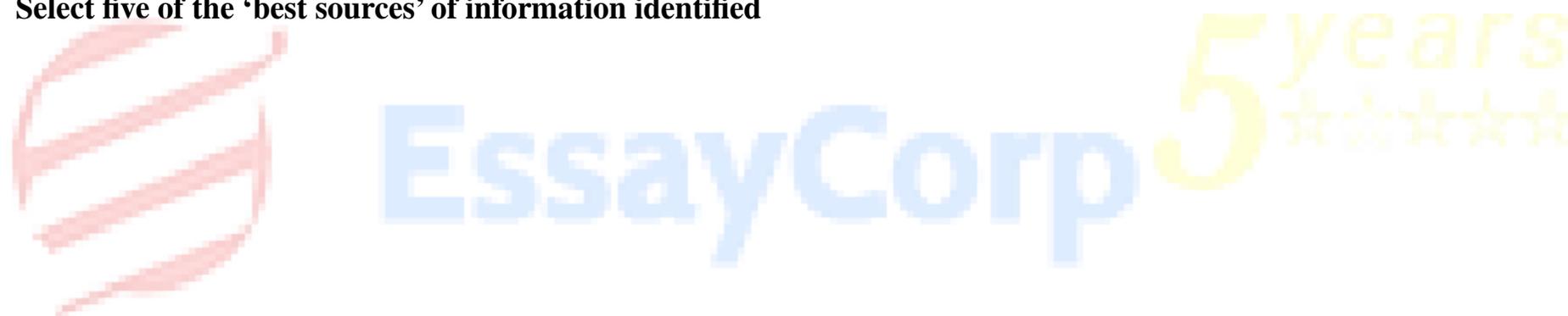
Is medical cannabis effective for treatment of chronic pain in adults?

Identify Databases Used	<input checked="" type="checkbox"/> Cochrane Library <input checked="" type="checkbox"/> PubMed/MEDLINE <input type="checkbox"/> JBI COnNECT+ (Joanna Briggs) <input type="checkbox"/> CINAHL with Full Text <input type="checkbox"/> CQUniversity Library Discover It! <input type="checkbox"/> Other (please Specify)
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Keywords		Search Terms	Alternative terms/synonyms
	P	Adults Chronic Pain	Chronic Pain, Pain adults
	I	Medical cannabis	Cannabinoids, Marijuana, Medical Marijuana
	C	No treatment	Control

	O	Treatment	Pain reduction, therapy, effect
Search filters or limits	<input checked="" type="checkbox"/> Age <input type="checkbox"/> Language <input type="checkbox"/> Publication years <input type="checkbox"/> Other (please specify)		

Select five of the ‘best sources’ of information identified



Citation (APA): Degenhardt, L., Lintzeris, N., Campbell, G., Bruno, R., Cohen, M., Farrell, M., & Hall, W.D. (2015). Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. *Drug and Alcohol Dependence, 1* (147), 144-150.

Level of evidence: Level II, Primary literature, Level 1.c of JBI (Joanna Briggs)

Annotation (100 words)

This article reported data from POINT (Pain and Opioids IN Treatment) study and included 1514 people from Australia who were prescribed a treatment of opioids for chronic pain (non-cancer). In this study they investigated the patterns of usage of cannabis. The study tried to correlate and assess the associations of demographic, pain etc among other patient characteristics and the subsequent use of cannabis for treatment of pain. The study came up with findings supporting that the use of cannabis for pain relief purposes is common in people having chronic pain (non cancer), and also report that the users experienced more pain relief when they used it along with opioids as compared to the usage of opioids

alone.

Citation (APA): Lynch, M.E. & Campbell, F. (2011). Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *British Journal of Clinical Pharmacology*, 72(5), 735-144.

Level of evidence: Level I, secondary literature, Level 1.a of JBI

Annotation (100 words)

This was a systematic review of randomized controlled trials available in the literature. A systematic review was conducted according to the PRISMA guidelines for reporting systematic reviews on the use of cannabinoids for treatment of chronic pain (non-cancer). The cannabinoids included in the systematic review included smoked cannabis, extracts of cannabis based medications (oralmucosal), nabilone, dronabinol along with a THC analogue. For the study they included patients with chronic non-cancer pain conditions like neuropathic pain, rheumatoid arthritis, fibromyalgia etc. This systematic review of randomized controlled trials provided evidence



supporting safety of cannabinoids in neuropathic pain along with giving preliminary evidence in rheumatoid arthritis and fibromyalgia.

Citation (APA): Russo, E.B. (2008). Cannabinoids in the management of difficult to treat pain. *Therapeutics and Clinical Risk Management*,

4(1), 245-259.

Level of evidence: Level I, secondary literature, Level 1.a of JBI

Annotation (100 words)

This article reviewed the present status of peer reviewed research on the randomized controlled trials on the use of cannabinoids for pain treatment and also cannabinoid analgesia involving both the endocannabinoid system and specific non-receptor pathways. The review focused on various cannabinoids like Tetrahydrocannabinol and nabilone which are approved in various countries but await approval for usage in pain treatment. The review also discussed synthetically manufactured counterparts of cannabinoids like ajulemic acid and Sativex[®], which is a derivative of cannabis which contains equal proportions of THC (partial CB₁) and cannabidiol. The review quotes that several methodologically structured randomized clinical trials have shown safety and efficacy of Sativex in chronic pain

complications like central, peripheral neuropathic pain, cancer, rheumatoid arthritis etc. The review gives good evidence that use of cannabinoids in adjunct to usual treatment of pain appears promising.

Citation (APA): Hill, K.P. (2015). Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *Journal of the American Medical Association*. 313(24), 2474-2483.

Level of evidence: Level III, secondary literature, Level 1.b of JBI

Annotation (100 words)

This was a clinical review on the pharmacological aspect, indications, and the legal issues associated with the use of marijuana for medical



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treatment. They reviewed the available medical literature on medical marijuana dated from 1948 up till March 2015 via a search of MEDLINE wherein they gave stress on randomized clinical trials (twenty eight) of cannabinoids usage as treatment for indications other than those established. The review came up with findings with high quality evidence in support of the medical marijuana usage for chronic pain, neuropathic pain etc. Several of the trials discussed in the review showed positive trends and suggested that marijuana or cannabinoids may be efficacious.

Citation (APA): Mather, L.E., Rauwendaal, E.R., Moxham-Hall, V.L., & Wodak, A.D. (2013). (Re)introducing medicinal cannabis. *Medical Journal of Australia*. 199(11), 759-761.

Level of evidence: Level VII, secondary literature, Level 5.c of JBI

Annotation (100 words)

This above mentioned debate published from NSW, Australia tried to look into medicinal utility of Cannabis based on its clinical efficacy, safety and cost-effectiveness. The report is based on several scientific evidence based studies which lead to the recommendation that medicinal cannabis can be used for treatment of pain and other medical complications like neuropathic pain with acceptable side effects. The report clearly states that the medical utility of cannabis has been ignored for long and the current actions by the state legislature to allow the usage (under strict recommendations) of medical cannabis was long overdue.

INTRODUCTION:

Chronic pain is a commonly occurring medical complication that may result from neuropathic origins, various cancers, HIV, cardiovascular disorders or invasive surgeries and therapies. The available therapeutic and pharmacological treatments for pain are scarce and basically ineffective. Medical Cannabis or medical Cannabinoids (derived) are the class of agents used for pharmacological interventions. It has been shown to be efficacious in conditions like nausea (following chemotherapy) and recently the interest has been generated for its use in treatment of chronic pain conditions. Data from studies on cannabinoid systems and their crosstalk with the endocrine pathways support the role of these



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cannabinoids as a potent analgesic. Use of medical cannabis as a therapeutic agent has been very restricted due to the ethical and legal issues involved. A very early systematic review by Campbell, Tramèr, Carroll, Reynolds, Moore & McQuay (2001) reported insufficient evidence and a need for more randomized controlled trials while the most recent ones identify their usage to be moderately beneficial in chronic pain management (Boychuk, Goddard, Mauro, & Orellana, 2015; Lynch & Campbell, 2011) . We conducted a structured literature review to determine evidence using the PICO model on usage of medical cannabis in chronic pain management in adults. PubMed and Cochrane Central Register of Controlled Trials were searched, with no language restriction. Search terms were reported and noted down. Various other data sources were also searched, including internet websites.

PART 2: LITERATURE REVIEW

Introduction

Chronic pain is a medical complication affecting around one of every five person world over. They basically are neuropathic or may be associated to various cancers, cardiovascular disorders or surgeries. The available treatment regimens have proved to be ineffective in chronic pain management in adults. Cannabis preparations have been used as a remedy for several years in traditional practices of medicine. Despite having

legal and ethical issues, cannabis can be seen a possible treatment alone in specific doses by clinicians or in adjunct to a multimodal treatment regimen, and the procedures for reintroduction of cannabis for chronic pain treatment in adults has be initiated (Mather, Rauwendaal, Moxham-Hall, & Wodak, 2013)

Evidence of searching the literature

Keywords: cannabinoids, cannabis, chronic non-cancer pain, chronic pain, neuropathic pain, adults

Databases used to search: PubMed/MEDLINE, Cochrane Library

Discussion

Pain management is a serious concern for most of the medical practitioners throughout the world as roughly one in five people in the developed world and in countries like Australia suffer from chronic pain. The problem of pain management is growing day by day and the current scenario needs some new and path breaking medications and pharmacological interventions. This chronic pain usually results from several debilitating diseases like HIV, cancers, other non-communicable cardiovascular diseases, surgery (invasive treatment), chemotherapy (used for treatment of diseases). Due to chronic pain patients are forced to live a poor quantity of life. Many pre-clinical and other experimental studies revealed that humans have specific cannabinoid receptors in the central nervous system as well as the peripheral nervous system and the detailed pathways of

these involved systems are yet to be revealed. Still the available studies show convincing trends. The studies assessed in the present literature review using the PICO model give us hope that cannabis or cannabis extracts can work as analgesics in pain management for chronic pain which is poorly managed otherwise.

Aims of most of the studies (which were mostly systematic reviews) was to carry out systematic review to check the utility and efficacy of medical cannabis or the extracts (cannabinoids) in the management of pain in various conditions like non-malignant and/or neuropathic condition (Boychuk, Goddard, Mauro, & Orellana, 2015; Lynch and Ware 2015). Some other clinical reviews and clinical reports explored the evidence for using cannabis and cannabinoids to manage pain (Wood 2004) using a non-systematic review format (Greenwell, 2012). The Randomised controlled trails assessed in this review were RCTs with varied designs like double-blind, placebo-controlled, crossover etc. They were aimed at assessing the usage of cannabis in HIV-associated distal sensory predominant polyneuropathy (Ellis et al., 2009) among others which were aimed at assessing the characteristics of patients with chronic pain who accessed treatment with medical cannabis (Aggarwal, Carter, Sullivan, ZumBrunnen, Morrill, & Mayer, 2009).

Most of the studies from literature were very detailed and methodologically strong. The earliest systematic review relevant to the topic was published by Campbell et al., (2001). The study gave a strong indication that there was a lack of studies and relevant RCTs are warranted as the available evidence in the form of reports, surveys and RCTs were insufficient to give a conclusive direction in this field to assess the uage of



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cannabis as an analgesic. This review could identify 18 trials that demonstrated a moderate degree of analgesic effect in various patients of chronic non-cancer pain, neuropathic pain, fibromyalgia and rheumatoid arthritis. They stated that Cannabinoids and cannabis extracts were not found to be more effective than codeine for pain management. Another review (Thaler, Gupta, & Cohen, 2011) provided a very detailed account of the cannabinoids usage using an in-depth examination protocol of the evidence supporting cannabinoids for pain management. The review also took into account the adverse events involved. They strongly supported the usage of cannabis in peripheral-neuropathic and central-pain conditions. The study also gave a word of caution stating that cannabinoids should be used in pain management only when safer medications have failed, or can be given as a component of a multimodal therapeutic regimen. A very relevant clinical review by Hill (2015) on the same PICO question reviewed the available literature on medical cannabis dated from 1948 up till March 2015 via a search of MEDLINE wherein they gave stress on randomized clinical trials (twenty eight) of cannabinoids usage as treatment for indications other than those established. The review came up with findings with high quality evidence in support of the medical marijuana usage for chronic pain, neuropathic pain etc. Several of the trials discussed in the review showed positive trends and suggested that marijuana or cannabinoids may be efficacious. A very recent systematic review (Boychuk, Goddard, Mauro, & Orellana, 2015) assessed the effectiveness of cannabinoid extracts in the management of chronic non malignant neuropathic pain wherein they assessed several studies in the literature which examined chronic neuropathic pain. The evaluation by the systematic review suggested that cannabis extracts may prove to be effective analgesics in chronic neuropathic pain conditions which have been refractory to other pharmacological treatments given to the patients.

A recent updated systematic review very aptly answered our research question. Lynch and Ware (2015) provided an updated systematic review of randomized controlled trials assessing cannabinoids for the treatment of chronic non-cancer pain. The review followed the PRISMA guidelines for systematic reviews reporting on health care outcomes. They suggested that the quality of the RCTs they examined were excellent and in fact seven trials reported good analgesic effect of cannabis. This review added further evidence in support of the safety of currently available cannabinoids as analgesics. A major randomized controlled trial by Degenhardt, et al., 2015 reported data from POINT (Pain and Opioids IN Treatment) study and included community samples from 1514 people from Australia who were prescribed a treatment of opioids for chronic pain

(non-cancer). In this study they investigated the patterns of usage of cannabis. The study tried to correlate and assess the associations of



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demographic, pain etc among other patient characteristics and the subsequent use of cannabis for treatment of pain. The study came up with findings supporting that the use of cannabis for pain relief purposes is common in people having chronic pain (non-cancer), and also report that the users experienced more pain relief when they used it along with opioids as compared to the usage of opioids alone.

While researching, we came across many types of studies like systematic reviews (Lynch & Ware, 2015; Boychuk, Goddard, Mauro & Orellana, 2015; Lynch & Campbell, 2011; Campbell, Tramèr, Carroll, Reynolds, Moore & McQuay, 2001), randomized controlled trials (Ellis et al., 2009), clinical reviews (Hill, 2015; Russo, 2008; Wood, 2004), clinical articles, descriptive studies, expert guidelines, opinions (Mather, Rauwendal, Moxham-Hall & Wodak 2013) and surveys (Swift, Gates and Dillon, 2005). Most of the systematic reviews discussed here assessed the effectiveness of cannabis and related cannabinoids in pain management in a randomized controlled setting. One study assessed the use of medicinal cannabis for neuropathic pain in study patients of HIV in a study design of a randomized, crossover clinical trial (Ellis et al., 2009).

Most of the evidence discussed here was supported by high-quality evidence and belonged to the Level I (JBI grading Level 1.a to Level 1.d) of the gradation i.e., most of the studies taken were systematic reviews or meta-analysis studies of randomized controlled trials. According to the weight and the gradation of the levels of evidence while answering a PICO model, the systematic reviews of RCTs are given maximum weight. Other studies like Randomised controlled trials, clinical reviews and clinical opinion, were also noted which belonged to various other levels of

evidence (Joanna Briggs Institute model).

Most of the studies included a structured methodology supported by good search strategies (in case of systematic reviews), comparable trial designs like cross-over parallel (in case of RCTs) and included most of the evidences available in published and unpublished sources at the time of their publications. As discussed above most of the studies belonged to the highest level of evidence. There were some limitations as well. The main limitations to the studies and their findings were usually short duration of the trials included in the study, small sample sizes of the studies



included in systematic review and low/modest effect sizes of the studies taken in to account (Lynch and Campbell, 2011). Larger trials on a large scale and multi-centric studies are needed to assess efficacy of medical marijuana usage keeping in mind the potential for abuse.

Recommendations

Usage of cannabis or cannabinoid extracts appears to be supported by good detailed systematic reviews and trials among people with chronic non-cancer pain, and can be advised by clinicians in combination with other medications or alone with keeping in caution the legal and ethical issues equally. Appropriate dosage determination for cannabis is also of prime importance. It is suggested that cannabis has an analgesic property equivalent to single dose of codeine 60 mg. And also constant increasing or stabilising the cannabinoid dose has to be taken in to

account for treatment of chronic pain in adult population.

Conclusion

Overall, on assessing these available evidences following a detailed literature search, we are in position to draw a conclusion. We may conclude that most of the systematic reviews of randomised controlled trials, give a very good degree of evidence in support of the usage of medical cannabis for the treatment of chronic pain in the current literature with keeping in mind the ethical and legal issues involved (as highlighted by most of the surveys and clinical reviews). The clinicians and healthcare workers should be encouraged to follow the strict guidelines while usage of medical cannabis, but despite its primary characteristic as an illicit drug, the pharmacological usage of medical cannabis has to be seen positively as evidenced by various systematic reviews, RCTs and surveys. The best evidence to answer this specific evidence based question would be the systematic reviews of RCTs (Lynch & ware, 2015; Boychuk, Goddard, Mauro & Orellana, 2015; Lynch & Campbell, 2011; Campbell, Tramèr, Carroll, Reynolds, Moore & McQuay, 2001).

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