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The Effectiveness and Safety of Cannabis/ Cannabinoids for Painful Diabetic Neuropathy: A Systematic Review

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Abstract

Objective: To evaluate the effectiveness and safety of cannabis/cannabinoids for painful diabetic neuropathy (PDN).

Design: Systematic review of interventional studies.

Data Source: Medline, PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL), AMED, PsycINFO, CINAHL, Web of Science and ScienceDirect, along with references from identified papers and grey literature search up to September 2017. Terms used were combined as follows: (marijuana OR marihuana OR cannabis OR cannabinoids) AND (painful neuropathy OR neuropathic pain) AND (Diabetes).

Study Selection: Studies of cannabis/cannabinoids, in adult participants diagnosed with PDN. Validity of trials was assessed using the Cochrane Collaboration's tool for assessing risk of bias.

Data Synthesis: Five studies that fit the inclusion criteria were identified.

Conclusion: Cannabis and cannabinoids provide an interesting treatment choice for PDN. Further high-quality studies with larger sample sizes and longer durations are required to assess its long-term effectiveness and safety as well as the best form of drug delivery.

Keywords: Painful diabetic neuropathy, Cannabis, Cannabinoids, Interventional studies

Introduction

The mechanism of Diabetic Peripheral Neuropathy (DPN) is not fully understood and attempts at identifying the underlying pathophysiology were unsuccessful due to a lack of neurological biomarkers required for assessing DPN risk factors (Haanpää and Hietaharju, 2013). Currently many conventional treatments for painful DPN rely on pharmacotherapy, for example mono or combination therapy with antidepressants, anticonvulsants or opiates (Cruccu, 2007). Many of these pharmacotherapies are considered suboptimal and can have unwanted adverse additional effects on the recipient (Haanpää and Hietaharju, 2013). It may be that future research can overcome this challenge by facilitating a better understanding of the pathogenesis of DPN to enable more precise pharmacological treatment targets. One such target could be the endocannabinoid and cannabinoid receptors (Toth *et al.*, 2012) renewing interest in the potential use of cannabis based agents for managing neuropathic pain.

Methods

Why Cannabinoids and Cannabis?

Whereas most current medications for neuropathy act upon ion channels, researchers have gained a new understanding of the pathophysiology of pain in animal

models due to the discovery of endocannabinoids and cannabinoid receptors (Toth *et al.*, 2012). Δ^9-THC is the main psychotropic component of cannabis, which results in limiting its therapeutic use as an isolated agent (Giacoppo *et al.*, 2014). However, several non-psychoactive cannabinoids have been identified, such as cannabidiol (CBD) (Earleywine, 2002; and Ben Amar, 2006). Hence, cannabinoids is a term used for compounds that mimic the effects of Δ^9-THC through activating the cannabinoid receptors (Chiou *et al.*, 2013). According to numerous animal models of pain, THC, its synthetic derivatives and CBD have analgesic effects (Mao *et al.*, 2000). Therefore, this newfound interest in its therapeutic properties resulted in the development of a number of cannabinoid-based synthetic medicines (Giacoppo *et al.*, 2014). However, there seems to be a dearth in literature investigating the extent of clinical significance their side effects might have on limiting treatment for neuropathic pain. This warrants further robustly constructed research in this area, hence the need to evaluate previous clinical trials addressing cannabis or cannabinoids as treatment options for the management of PDN (Wallace *et al.*, 2015).

The Research Question

The following research question was set: '*What evidence is available regarding the use of cannabis/cannabinoids as treatment options for the management of PDN in clinical and long term settings?*'

Once broken down into a series of relevant but more specific objectives, the preliminary aims of conducting this systematic review are to evaluate:

- The effectiveness of cannabis/cannabinoids as part of the treatment for management of pain in patients with PDN.
- The safety of cannabis/cannabinoids in the treatment of PDN.

Search Strategy

For the purpose of a systematic review, terms used in this literature search were combined and the search term selected and agreed upon as follows: (marijuana OR marihuana OR cannabis OR cannabinoids) AND (painful neuropathy OR neuropathic pain) AND (Diabetes).

Figure 1: Literature Review Flowchart

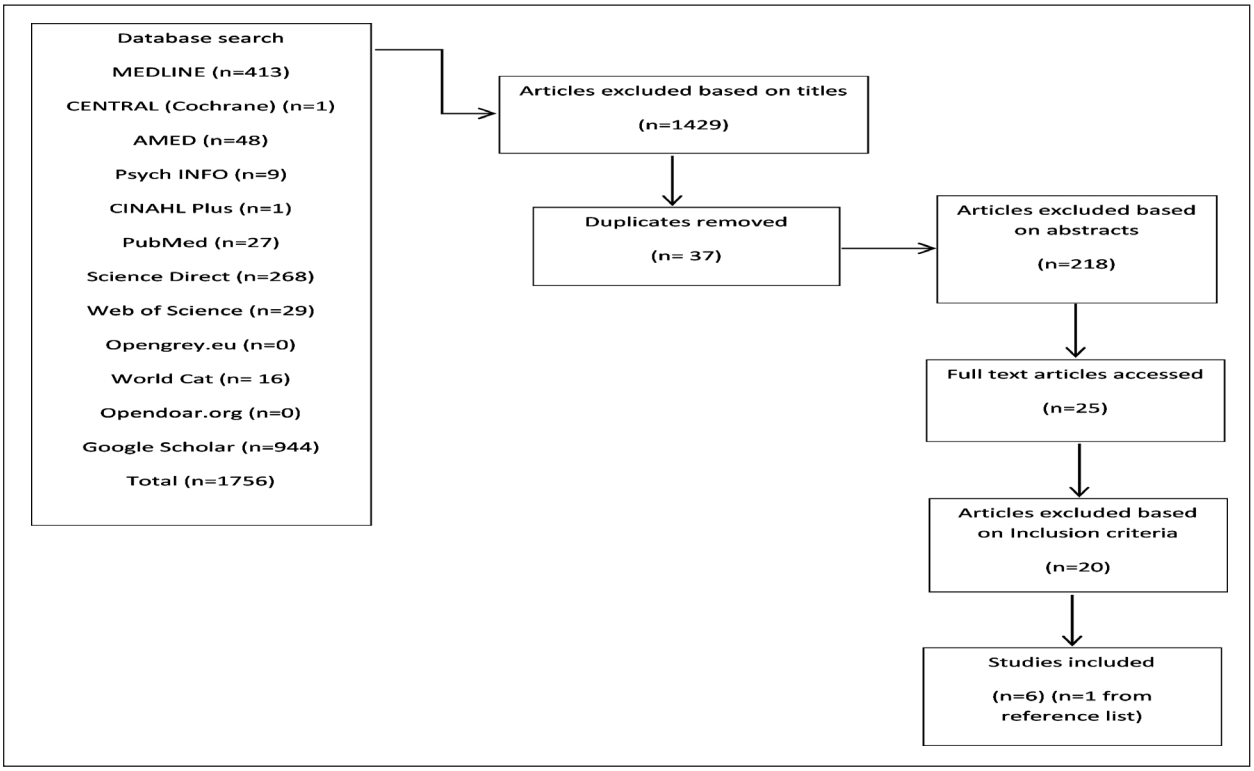


Table 1: Literature Review for Systematic Reviews

Databases for Systematic Reviews	Date	Results	Possible Relevant Results
Database of Abstracts of Reviews of Effects (DARE)	16/05/2017	0	0
Cochrane Database of Systematic Reviews (CDSR)	16/05/2017	2	1
the NIHR Health Technology Assessment (NIHR HTA)	16/05/2017	0	0
National Institute for Health and Clinical Excellence (NICE)	16/05/2017	36	0
Evidence for Policy and Practice Information (EPPI) Centre, which has a database of systematic reviews of public health interventions (DoPHER)	16/05/2017	0	0
Scottish Intercollegiate Guidelines Network (SIGN)	16/05/2017	0	0
National Guidelines Clearinghouse (NGC)	16/05/2017	0	0

Table 2: Search Strategy for Grey Literature

Databases for Grey Literature	Date	Results	Possible Relevant Results
Opengrey.eu	28/05/2017	0	0
WorldCat	28/05/2017	16	8
Opendoar.org	28/05/2017	0	0
Google Scholar	28/05/2017	944	220

Table 3: Inclusion/Exclusion Criteria

Population	Studies of adult participants diagnosed with painful diabetic polyneuropathy and on a stable regimen of diabetic therapy. Pre-clinical and animal studies as well as studies concerning children were excluded.
Interventions	Cannabis or cannabinoids administered by whichever route of administration (experimental intervention) with any analgesic or placebo (control intervention).
Outcomes	Positive (pain intensity scores, pain relief scores) or adverse health based outcomes.
Study design	As this area of research is relatively underdeveloped, a systematic review of such a topic had to include evidence from studies with a range of designs due to the limited number of studies available.
Language	This systematic review included studies in any language. All results in non-English languages provided translated abstracts, however (n= 0) of non-English papers met the inclusion criteria for this review.
Study design	Comparative studies examining the analgesic affects in at least two population groups primarily randomised controlled trials (RCTs) and controlled trials. However, if information from controlled trials is not available, cohort studies may be included if there is a record of data from a comparison group. However, due to the specific population sample, only controlled trials were found and two narrative reviews were identified, which only narratively review and do not rank evidence, hence, were excluded.
Settings	Hospital wards- rehabilitation centres- nursing and residential respite centres- hospices.
Time frame	No limit.

Table 4: Studies Included in the Systematic Review

No.	Author	Date of Pub.	Title of Study	Design of Study	Critical Appraisal Tool Used
1.	Hoggart, B.	2015	A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain	Open label follow on study	The risk of bias assessment tool was developed for Cochrane (2008), the risk of bias' assessment tool, which considers the results of the trial, the validity of the results, and whether they can be applied to the local population.
2.	Toth, C.	2012	An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of Nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain	Adjuvant study	
3.	Selvarajah, D.	2010	Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex®) in painful diabetic neuropathy: Depression is a major confounding factor	RCT	
4.	Wallace, M. S	2015	Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy	RCT	
5.	GW Pharmaceuticals Ltd. (Principal investigator: Solomon Tesfaye)	2012	A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy	RCT	

Using the review selection criteria, The results from multiple electronic databases are presented in Figure 1 as a flow chart and summarised in Table 1. Finally, a manual search of journals and reference lists of the selected studies was performed to identify further studies (n=1). A search for grey literature was also performed (see Table 2).

Assessing Methodological Quality and Data Extraction

Study Review: Abstracts returned from the search results were independently reviewed by the primary researcher to determine whether they satisfied the inclusion criteria (Table 3). Uncertainty was resolved by consensus with the research team

Data Extraction: Using a standardised data collection electronic form summarized in terms of study design, participants, method of intervention, and study outcomes of the included studies in Table 4.

Risk of Bias (Quality) Assessment: Using the Cochrane Collaboration's tool for assessing risk of bias (2008), Table 5 explores heterogeneity, suitability of meta-analysis and any flaws in studies which may bias the results reported.

Study Characteristics/Appraisal

Out of five studies, only one Randomised Controlled Trial (RCT) (Wallace *et al.*, 2015) discussed the efficacy of inhaled cannabis on pain and hyperalgesia of patients with PDN. There were 16 participants in the

Table 5: Cochrane Collaboration's Tool for Assessing Risk of Bias

Study	RISK OF BIAS						
	Random Sequence Generation	Allocation Concealment	Participant/ Personnel Blinding	Assessor Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Outcome Overall
Wallace *et al.*, 2015	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	High risk of bias	High risk of bias
Selvarajah *et al.*, 2010	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias
GW Pharmaceuticals Ltd., 2012	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	High risk of bias	Low risk of bias	High risk of bias
Hoggart *et al.*, 2014	High risk of bias	High risk of bias	High risk of bias	High risk of bias	Unclear	Unclear risk of bias	High risk of bias
Toth *et al.*, 2012	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	High risk of bias

study, all of them being 18 years old and above, and presented with PDN. The other four studies (Selvarajah *et al.*, 2010; Toth *et al.*, 2012; GW Pharmaceuticals Ltd., 2012; and Hoggart *et al*., 2014) discussed the use of cannabinoids in the management of PDN. One study, conducted in Canada (Toth *et al.*, 2012) used an oral cannabinoid Nabilone as an adjunctive treatment; the selected population sample was specified (patients with refractory DPN). The total number of participants in this study was 37 with an age range of 18 or above. The three final studies (Selvarajah *et al.*, 2010; GW Pharmaceuticals Ltd., 2012; and Hoggart *et al.*, 2014) used (THC/CBD) oromucosal spray Sativex® as the intervention method. In total there was 389 participants who completed the studies, with numbers ranging from 30 to 264 (age range 18 or above). Each study employed different methods and participant-criteria ranged. Two studies (Selvarajah *et al.*, 2010; and GW Pharmaceuticals Ltd., 2012) were performed in the UK, while one study (Hoggart *et al.*, 2014) was performed at clinics in five different countries (Romania, UK, Canada, Belgium and Czech Republic). Out of the five studies, it was unclear whether the researchers took into account confounding factors in design analysis, except for one RCT (Selvarajah *et al.*, 2010). Additionally, it was unclear whether there was follow up long enough to establish long-term effects of the interventions used except for one study (Hoggart *et al.*, 2014). In conclusion, due to the small number of studies and the variation in interventions and outcomes, pooling of data for meta-analysis was inappropriate. Results were therefore reported and summarised descriptively.

Results

Risk of Bias

Four trials were judged at high risk of bias, and one study at unclear risk of bias (Selvarajah *et al.*, 2010). This highlighted several limitations including failure to appropriately handle withdrawals, selective outcome reporting, and inadequate description of methods of randomization, allocation concealment, and blinding (Whiting *et al.*, 2015). The major limitations to the findings of this review are the small number of included studies, small sample size and short trial durations. Moreover, none of the trials provided details of the concomitant analgesics taken by their participants (except for the study of Hoggart *et al.*, 2015). Furthermore, none of the trials provided evidence to support the appropriateness of the sample size. Therefore, in order to reach conclusions regarding the efficacy, safety and potential for abuse, trials of longer duration with larger sample sizes are needed.

Effects on Pain

Only one trial examined the effects of inhaled cannabis on PDN (Wallace *et al.*, 2015) and revealed a dose-dependent effect of vaporized cannabis on spontaneous pain; therefore, the outcome was positive ($P < 0.001$). Four studies examined the effects of cannabinoids on PDN. Two of those studies (GW Pharmaceuticals

Ltd., 2012; Selvarajah *et al.*, 2010), reported overall negative outcomes. The findings of Selvarajah et al. (2010) did not exhibit significant differences of reduction in the two primary outcome measures (change in mean daily pain scores and Neuropathic Pain Scale scores (P = 0.62; 7.8; -20.1 to 12.1). Furthermore, no significant difference in mean change TPS (total pain score) at end point between Sativex® and placebo was exhibited (P = 0.40; SEM 9.5; 95% CI -11.3 to 27.8). The study undertaken by GW Pharmaceuticals Ltd. (2012) was never published; however, results obtained from the website (https://clinicaltrials.gov) did not report any significant differences between Sativex® and placebo on any of the measure outcomes. Regarding the study by Hoggart *et al.* (2014), 234 (70%) participants reported clinically significant nerve pain reduction (minimum 30% reduction) and also exhibited 50% cumulative improvements in pain with time. The authors also concluded that the drug is effective since most participants completed the 9 month trial of treatment with Sativex® without an increase in the number of adjunctive analgesic medications. Therefore, the overall outcome was positive for this study. Toth *et al.* (2012) reported that reduction in pain intensity greater than 30% (ANOVA, P < 0.05) and 50% (ANOVA, P = NS) was significantly greater in the group receiving flexible dosing of Nabilone compared to the placebo group; hence, this was a positive outcome.

Adverse Effects

Wallace *et al.* (2015) reported that with the high (7% THC) dose cannabis, a significant effect of impaired performance on 2 of the 3 neuropsychological tests was observed. Euphoria was observed at 100% for participants on the high dose of cannabis and at 60% for those on placebo. Furthermore, the only group of participants that reported a larger percentage of somnolence than placebo was the group on high (7% THC) dose cannabis (P= 0.018). With respect to cognition, the PASAT (Paced Auditory Serial Addition Test) tool (Gronwall, 1977) was used to measure attention and working memory. The majority of the scaled score differences were less than 1.5 points lower than baseline and no scores below 8 were observed. This would indicate that for this group the cognition did not decline dramatically into the impaired range.

In the Hoggart *et al.* (2014) trial, 78% (n=295) experienced at least one Adverse Effect (AE). 59% (n=224) were considered treatment-related and the most commonly reported were dizziness (19%), nausea (9%), dry mouth (8%), dysgeusia (7%), fatigue (7%), somnolence (7%) and feeling drunk (6%). 11% of (n=40) patients had serious AEs during the study however, only 1% (n=4) were considered treatment related [amnesia (n=2), paranoia (n=1) and suicide attempt (n=1)]. There were no significant differences observed in the incidence of AEs reported in relation to the patients' mean daily dose. Patients that withdrew from the study due to AEs were 23% (7% severe AEs and 18% treatment related AEs). However, according to the authors of this study, only a small percentage withdrew due to lack of efficacy.

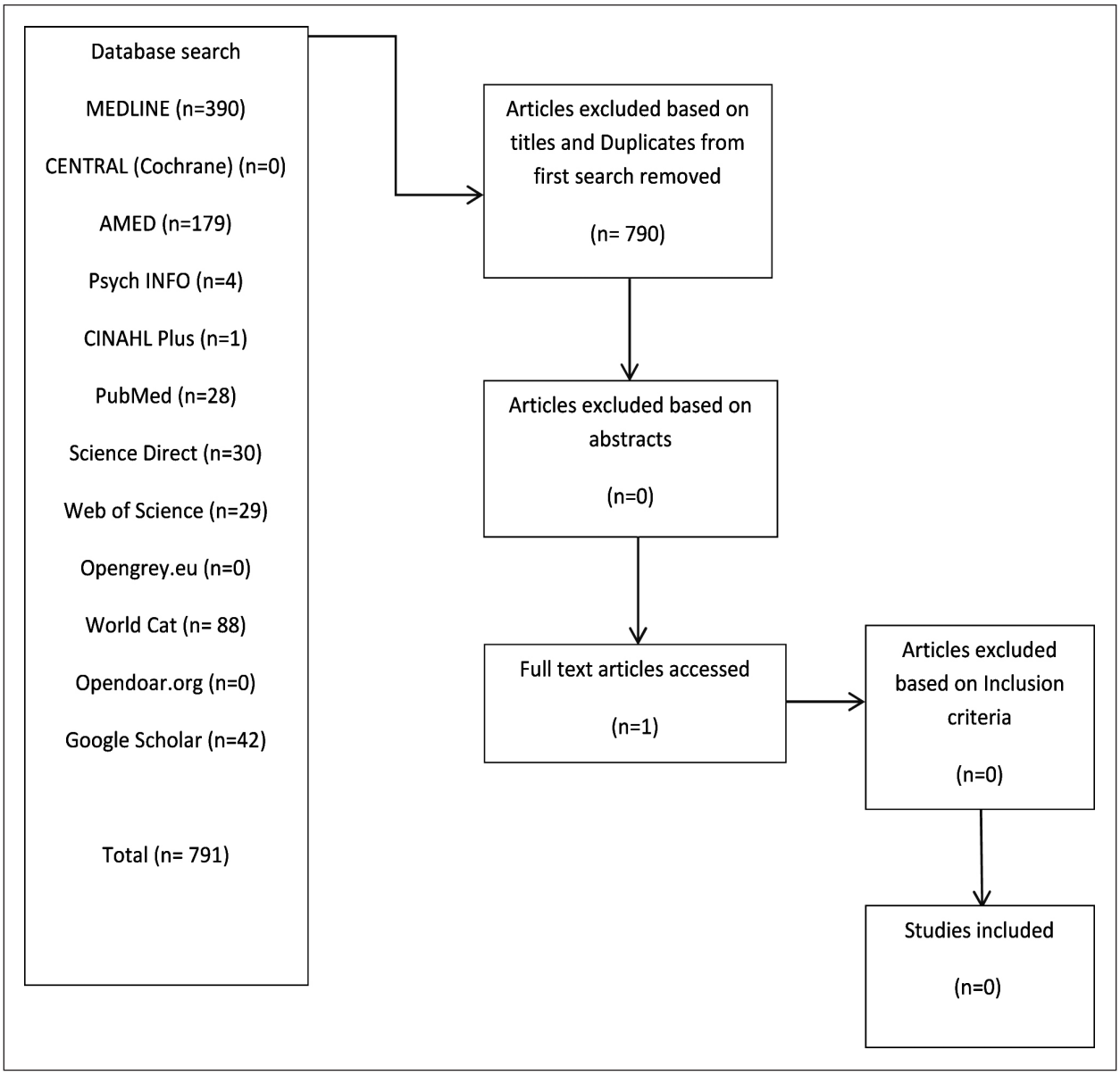
Toth *et al.* (2015) reported a number of potentially treatment-related AEs including dizziness, dry mouth, drowsiness, confusion or impaired memory, lethargy, euphoria, headache, and increased appetite. Most were considered either mild or moderate. However, in the single-blind phase, two participants receiving Nabilone at doses of 2 mg daily and 4 mg daily reported serious AE (intolerable confusion), which led to their discontinuation from the study. In the double-blind phase, a total of 46% (n=6/13) of participants receiving placebo and 54% (n=7/13) of subjects receiving Nabilone reported treatment-related AEs. In the study of Selvarajah *et al.* (2010), 6 participants withdrew because of AEs. However, it was not mentioned whether any were treatment related or serious AEs.

Limitations

Searching for grey literature was challenging due to practical issues limiting the inclusion of all studies regardless of publication type/status (CRD, 2009). Conference abstracts and interim results were not considered due to the difficulty of appraising their quality from the minimal detail provided and contacting authors to obtain the full details of studies was not possible due to time restraints. Moreover, there were two studies that were obtained via interlibrary loan not in a readable form, which prevented the full text assessment during the selection process for this review.

The first search results highlighted an alternative spelling to marijuana "marihuana" which could have had an impact on the validity of the data. Since this was an identification of a flaw in the search term prior to completion of the systematic review, the original term had to be altered in order to re-run the searches

Figure 2: Literature Review Flowchart of Modified Search Term



to ensure that no data was missed shown in Figure 2. The terms Charas and Hashish are used for a different preparation than marijuana (Earleywine, 2002), therefore were excluded in the search term. However including them might have provided a larger number of relevant search results.

The traditional approach to neuropathic pain management has been to classify and treat it based on the aetiology of the underlying pathology. Evidence suggesting the use of a mechanism-based approach when classifying neuropathic pain has potential benefits such as individualizing therapy and facilitation in testing new therapies (Dworkin *et al.*, 2003). Therefore, recruiting participants using a mechanism-based approach in future clinical trials might yield larger sample sizes for future reviews.

In addition, the number of researchers that performed data extraction and quality appraisal was influenced

by time restrictions. Therefore, the ideal methodology had to be adjusted to fit the timeframe and resources available for this study, whilst maintaining the robustness. Finally, due to the poor heterogeneity of the available retrieved data, no meta-analysis was performed, as this method was not suitable to the types of data retrieved during this review.

Discussion and Clinical Implications

More studies examined the effects of cannabinoids (n=4) than inhaled cannabis (n=1). The two pharmaceutical preparations of cannabinoids investigated in this review are Nabilone (synthetic analogue of THC) or Sativex® (THC+CBD). Both have different pharmacokinetic profiles; Nabilone has a bioavailability of 60%, whereas the bioavailability of Sativex® is not well documented (CPA, 2005). The route of administration for Sativex® sublingual spray compared to the oral route decreases the first-pass metabolism, increasing the bioavailability and therefore dose-titration of the drug (Pryce and Baker, 2005). On the other hand, oral cannabinoids such as Nabilone have a slower onset of action, lower peak drug concentrations and slow, unpredictable and more erratic absorption when compared to inhaled cannabis. Moreover, it was reported that the bioavailability of the drug after oral administration varied between individuals. This not only indicates that it has an unreliable onset of action (Ashton, 2001; and Ben Amar, 2006), but also that some individuals are more sensitive to the drug via oral administration than others, therefore defining a dose may not be standardised for oral administration. THC blood concentrations after oral route administration were found to be 25-30% of THC blood concentrations after smoking an equal dose indicating that symptoms are more rapidly relieved with inhaled cannabis (Ashton, 2001). However, the bioavailability of inhaled cannabis (THC) ranges from 18 to 50% and has a rapid onset of action (3-5 min) (Ben Amar, 2006). Inhaled cannabis also contains other substances besides THC, which might facilitate an increase in the effects of THC and modulate its side effects (Carter *et al.*, 2004). For example CBD is known to act synergistically with THC in addition to reducing the psychotropic effects of THC (Russo and Guy, 2006). Moreover, some experienced patients prefer inhaled cannabis because it enables them to have more control over the appropriate dose required to control their symptoms (Abrams *et al.*, 2003). However, inhaled cannabis in cigarette form has more harmful effects than oral administration as the long term risk of being affected by pharyngitis, rhinitis, asthma, bronchitis, emphysema and lung cancer is greater for marijuana smokers (Hall and Solowij, 1998). Moreover, consistency in findings was reported (Haire-Joshu, Glasgow and Tibbs, 1999) demonstrating smoking for people with diabetes increased the risk for microvascular and macrovascular disease and premature mortality. Therefore, with the increasing interest in medical cannabis use, smoked cannabis seems to be the preferred method of administration by patients but cannot be recommended due to the aforementioned co-morbidity implications. As a result, interest developed for an alternative technique of cannabis inhalation via the electric powered vaporization of cannabis without the production of potentially toxic products of smoking such as tar, carbon monoxide, and other carcinogens (Hazekamp *et al.*, 2006). Current trials investigating medical marijuana are finding vaporization as an attractive delivery method for research instead of cannabis in cigarette form (Wallace *et al.*, 2015). Furthermore, the pharmaceutical industry also has become interested in developing and investigating alternative formulations of cannabinoids such as smokeless oral inhalers (aerosols), nasal sprays (Cannatol Rx, 2016), transdermal patches (Stinchcomb *et al.*, 2004) and rectal suppositories (Brenneisen *et al.*, 1996).

The longest trial (Hoggart *et al.*, 2014) included in this review (a 9-month open-label, follow-on study) reported no evidence of the development of tolerance towards THC/CBD spray, with the median number of daily sprays of THC/CBD spray reducing from 8.0 daily sprays after 1 month of treatment to 6.6 daily sprays during the last month of treatment. However, the only included study (Wallace *et al.*, 2015) investigating the efficacy of inhaled cannabis on PDN, was a single dose, short-term study that could not provide conclusions regarding the long term tolerability, reporting it as an area that requires further research. Therefore, it is apparent that to date, far less numbers of controlled trials have been conducted to investigate cannabis in the inhaled form. More trials of inhaled cannabis may be achieved with access to medical grade cannabis for research purposes and interest from pharmaceutical companies to include this form of cannabis preparation in their research.

While statistical reduction in pain was reported in three studies, a more relevant and important outcome is the clinically meaningful pain reduction. This is defined as a reduction of 2 points on a 0-10 numerical pain scale or 30% reduction in pain intensity (Dworkin *et al.*, 2008). Only 2 of the 3 studies reported positive findings in this respect. The majority of the included studies were placebo-controlled (n=4), however this is found to be problematic when investigating drugs with psychoactive properties such as cannabis and cannabinoids. The study of Selvarajah *et al.* (2010) was able to identify depression as a primary confounder affecting its outcomes, which possibly demonstrates the strong link of depression with pain perception (Frisher *et al.*, 2010). On the other hand, it was stated that there was a significant effect of depression on Total Pain Score (TPS), which was defined as an average score of the following three pain modalities: superficial, deep and muscular pain. However, the authors did not provide definitions of these three pain modalities or supportive evidence of existing association between them and DPN and whether TPS was considered as a valid measuring tool for PDN. Furthermore, it was not clear in the study whether the depression identified was associated with DPN.

The success of blinding in trials largely depends on the type and nature of the intervention used (CRD, 2009). For interventions such as cannabis, true blinding might not be achievable due to its psychoactive effects. The two trials with crossover designs (Toth *et al.*, 2012; and Wallace *et al.*, 2015) have identified this potential lack of blinding. Furthermore, the placebo response in the study of Wallace *et al.* (2015) was reported as larger than most trials of painful neuropathy, which suggests that the anticipated psychoactive effects might have resulted in decrease of pain unrelated to marijuana. This in return might affect the outcome and statistical analysis of the findings. It is also important to note that since Hoggart *et al.* (2014) did not include a placebo for comparison, the observed maintenance of efficacy with the Sativex® spray could be due to other factors such as changes in the underlying disease over time, changes in the set of participants, and efficacy related withdrawals.

Furthermore, all studies included did not exclude concomitant treatments. Researchers have an ethical obligation towards participants in their studies, as they must avoid causing them harm (beneficence) and strive to maximise the possible benefits of the research. Therefore, it is unethical to terminate treatments benefitting the patient (National Advisory Council on Drug Abuse (NACDA, 2006). However, the use of concomitant medications may be a confounding factor affecting the results of efficacy and toxicity even if the intervention method was proposed for adjunctive use in DPN studies. Therefore, the results produced might not represent true values. Finally, this systematic review did not identify any effectiveness studies comparing the outcomes with the traditional treatments available for PDN. These types of studies would be beneficial in specifying the role that cannabis and cannabinoids would have in the management of PDN.

Conclusion

Neuropathic pain is difficult to manage (Committee for Medicinal Products for Human Use (CHMP), 2004) and less than 50% of patients receive clinically meaningful benefit with the available drugs (Attal *et al.*, 2010). Recently, there has been increased interest in investigating the analgesic properties of cannabis and cannabinoids on neuropathic conditions, and study findings have been consistent and reproducible (Wilsey *et al.*, 2013). Only one trial examined the effects of inhaled cannabis on PDN (Wallace *et al.*, 2015) with a positive outcome ($P < 0.001$). Four studies examined the effects of cannabinoids on PDN and two of those studies (Selvarajah *et al.*, 2010; and GW Pharmaceuticals Ltd., 2012), reported overall negative outcomes. It was unclear whether there was follow up long enough to establish long-term effects of the interventions used except for one study (Hoggart *et al.*, 2014). Therefore, more robust studies with bigger sample sizes are needed to confirm these findings, as current evidence on the effects and adverse effects of cannabis are minimal. Since different preparations of cannabinoids exist for DPN and other neuropathic conditions, further large RCTs are required to determine the most suitable cannabinoid for each neuropathic condition and the most appropriate route of administration in order to maximise the beneficial effects and minimise the incidence of adverse effects. Furthermore, larger randomised trials with longer durations and longer term follow up are necessary to evaluate the long term effects, safety and tolerability of cannabis and cannabinoids as analgesics for PDN. Researchers conducting

cannabis or cannabinoids trials in the future should keep in mind the value of evaluating outcomes that are relevant to patients, using standardised outcome measures. They should also take into consideration the most adequate methods to use to allow appropriate randomisation, blinding, concealment of allocation and handling of withdrawals to avoid selective outcome reporting.

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