The Effectiveness of Cannabinoids in the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Review

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Aims: To carry out a systematic review to assess the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain. **Methods:** Electronic database searches were performed using Medline, PubMed, Embase, all evidence-based medicine reviews, and Web of Science, through communication with the Canadian Consortium for the Investigation of Cannabinoids (CCIC), and by searching printed indices from 1950. Terms used were marijuana, marihuana, cannabis, cannabinoids, nabilone, delta-9-tetrahydrocannabinol, cannabidiol, ajulemic acid, dronabinol, pain, chronic, disease, and neuropathic. Randomized placebo-controlled trials (RCTs) involving cannabis and cannabinoids for the treatment of chronic nonmalignant pain were selected. Outcomes considered were reduction in pain intensity and adverse events. **Results:** Of the 24 studies that examined chronic neuropathic pain, 11 studies were excluded. The 13 included studies were rated using the Jadad Scale to measure bias in pain research. Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments. **Conclusion:** Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments. Further high-quality studies are needed to assess the impact of the duration of the treatment as well as the best form of drug delivery. *J Oral Facial Pain Headache 2015;29:7–14. doi: 10.11607/ofph.1274*

Key words: *cannabinoids, chronic nonmalignant pain, management, neuropathic pain, systematic review*

The use of cannabinoids in treating various conditions dates back thousands of years in Eastern traditional medicine[1] and was introduced to Europe in the 1800s.[2] The medical use of cannabis fell from favor in the 1930s and 1940s for a number of reasons, including the development of more predictable medications.[1,2] Over the past several decades, there has been a renewed interest in the medical use of cannabis for a variety of conditions, including pain.[3,4] Historically, pain has been viewed as a symptom of more serious medical conditions, but more recently chronic pain has itself been regarded as a complex illness.[5,6] Existing nonsteroidal anti-inflammatory drugs are frequently ineffective, while currently available opioid medications have numerous adverse effects and are not always effective in specific types of chronic pain.[5]

The earliest clinical studies that evaluated the antinociceptive properties of cannabinoids were limited by an inadequate sample size and an insufficient assortment of cannabinoids available for use.[7] Of the numerous cannabinoids that have been identified in the cannabis plant, cannabidiol (CBD) and delta-9-tetrahydroxycannabinol (THC) and its synthetic derivatives are the most active in humans.[4]

Earlier reviews of the medical use of cannabinoids in pain therapy have been based on small sample sizes,[7–9] did not include adequate differentiation of the origins of pain syndromes,[10,11] and lacked identification of cannabinoid responders.[11] They also have failed to adequately assess the clinical relevance of effects,[12] safety profiles,[13] adverse events,[11,14] and long-term consequences,[13] although they have generally

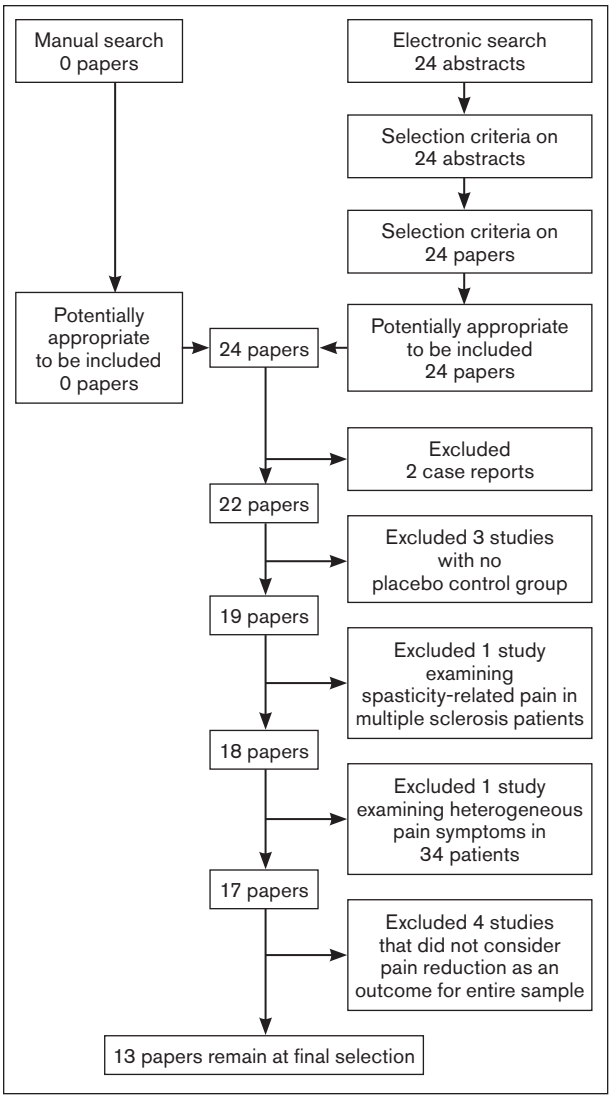

Fig 1 Flow diagram of the literature search.

considered cannabinoids to be "promising."[10–13] The most recent systematic review[15] included clinical trials of cannabinoids for chronic neuropathic pain, but also for chronic (non-cancer) pain related to fibromyalgia, rheumatoid arthritis, and mixed sources. Furthermore, it included a trial solely comparing a cannabinoid with an active control group (dihydrocodeine) and no placebo control group[16] and two trials where pain was not the primary symptom targeted for each subject.[17,18] Moreover, additional studies have been published since this systematic review, including one that utilized novel delivery methods[19] and two that used enriched enrollment to study only those patients deemed responsive to cannabinoid extracts.[20,21]

Therefore, the primary objective of the present systematic review was to determine the effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain. A secondary aim was to summarize adverse events, as there appears to be a degree of contention in regard to their severity.

Materials and Methods

The following terms were used to identify high-quality articles among the published abstracts:

- Human clinical trials
- Chronic nonmalignant neuropathic pain
- Cannabis or cannabinoids as active agent(s)

A computerized search was then conducted using PubMed (1966 to April 30, 2013), Embase (1988 to April 30, 2013), Web of Science (1945 to April 30, 2013), and all evidence-based medicine reviews and databases (Cochrane Database of Systematic Reviews, ASP Journal Club, Database of Abstracts of Reviews of Effects [DARE], and Cochrane Controlled Trials Register [CCTR]) (to April 30, 2013) for cannabis/cannabinoids and pain. Terms used in this literature search were combined as follows: (marijuana OR marihuana OR cannabis OR cannabinoids OR nabilone OR delta-9-tetrahydrocannabinol OR cannabidiol OR ajulemic acid OR dronabinol) AND (pain OR chronic OR disease OR neuropathic). A flow diagram of the literature search is shown in Fig 1.

Two researchers determined the eligibility of articles and selected them by analyzing the title and abstracts of each article. All the articles that met the inclusion criteria based on their abstracts were selected and collected. Discrepancies between the two researchers were resolved through evaluation by a third researcher. Once the actual articles were obtained, the final selection was independently completed by two researchers who evaluated each article and compared their results. The use of an adequate control group to factor out placebo effect, randomization of the sample, and double blinding of the primary investigator and subjects were considered as inclusion criteria at this stage of the selection process, as defined within the context of the Jadad scale,[22] which was used to rate the quality of the articles. Any discrepancies were settled through evaluation by a third researcher. As well, reference lists of the selected articles were hand-searched for additional relevant publications that may have been overlooked during the database searches. In cases where specific data was necessary for the discussion, and was not specified in the article, efforts were made to contact the authors to obtain the required extra information.

Table 1 Search Results from Different Databases

Database	Search terms	Results	Selected	Percentage of total selected abstracts*
PubMed	marijuana OR marihuana OR cannabis OR cannabinoids OR nabilone OR delta-9-tetrahydrocannabinol OR cannabidiol OR ajulemic acid OR dronabinol AND pain OR chronic OR disease OR neuropathic	3,870	13	100
Medline	marijuana OR marihuana OR cannabis OR cannabinoids OR nabilone OR delta-9-tetrahydrocannabinol OR cannabidiol OR ajulemic acid OR dronabinol) AND pain OR chronic OR disease OR neuropathic	3,870	13	100
Medline in-process and other non-indexed citations	marijuana OR marihuana OR cannabis OR cannabinoids OR nabilone OR delta-9-tetrahydrocannabinol OR cannabidiol OR ajulemic acid OR dronabinol AND pain OR chronic OR disease OR neuropathic	43	13	100
Embase	marijuana OR marihuana OR cannabis OR cannabinoids OR nabilone OR delta-9-tetrahydrocannabinol OR cannabidiol OR ajulemic acid OR dronabinol AND pain OR chronic OR disease OR neuropathic	1,122	12	100
all EBM reviews (Cochrane Database of Systematic Reviews, ASP Journal Club, DARE, and CCTR)	marijuana OR marihuana OR cannabis OR cannabinoids OR nabilone OR delta-9-tetrahydrocannabinol OR cannabidiol OR ajulemic acid OR dronabinol AND pain OR chronic OR disease OR neuropathic	113	7	58
Web of Science	marijuana OR marihuana OR cannabis OR cannabinoids OR nabilone OR delta-9-tetrahydrocannabinol OR cannabidiol OR ajulemic acid OR dronabinol AND pain OR chronic OR disease OR neuropathic	1,201	12	100

*Percentages do not add up to 100% because the same reference could be found in several databases. EBM = evidence-based medicine; DARE = Database of Abstracts of Reviews of Effects; CCTR = Cochrane Controlled Trials Register.

Results

Identification of Studies

The search results and the final number of abstracts selected from the various databases are provided in Table 1. When comparing the database results, it was found that Medline, PubMed, Embase, and Web of Science repeated all of the abstracts. CCTR included 6 abstracts and ACP Journal Club contained 1 abstract, all of which were repeated in Medline, PubMed, Embase, and Web of Science. The authors did not obtain any further hits from communication with the Canadian Consortium for the Investigation of Cannabinoids (CCIC), nor did they obtain any further hits from an Internet search of websites for the International Association for the Use of Cannabis as Medication (IACM), GW Pharmaceuticals, and the International Association for Cannabis Research. After the complete articles of the 24 abstracts initially selected were read, only 13 fulfilled the initial selection criteria. Manual searching of the references from these 13 studies did not reveal any study that had not appeared in the electronic search.

Eleven of the 24 articles were rejected for the following reasons: One was rejected because it was a case report that involved only one patient and it dealt with inflammatory as opposed to neuropathic pain.[23] Another was rejected because it was a case report that included only one subject who underwent multiple interventions.[24] Another was rejected because it consisted of 34 "n of 1" studies with patients who were not suffering exclusively from neuropathic pain.[25] Rather, the primary pain symptoms were heterogeneous in nature and two patients described primary symptoms that were not painful in nature (tremor and bladder urgency). Three studies were rejected due to lack of a placebo control group.[16,26,27] Four studies (that examined the effects of cannabinoids on multiple sclerosis symptoms) were excluded because they considered pain reduction as an outcome for only a portion of their samples,[17,18,28,29] and one study was excluded because it examined spasticity-related pain in multiple sclerosis patients.[30] Summaries of the 11 articles that were rejected are displayed in Table 2.

Upon elimination of the aforementioned studies, 13 remained for inclusion in the systematic review.[19–21,31–40]

The cannabinoids administered for neuropathic pain therapy fall into three groups: whole plant, extract, and synthetic. The whole plant cannabinoids are delivered as smoke or vapor, the extracts are delivered as an aerosol spray, and the synthetic cannabinoids are ingested orally. Of the 13 studies analyzed in the systematic review, 10 examined phytocannabinoids

Table 2 Studies that Fulfilled Initial Selection Criteria but Were Later Rejected

Authors	Reason(s) for rejection
Holdcroft et al[23]	Case report
Maurer et al[24]	Case report
Notcutt et al[25]	Case reports
Clermont-Gnamien et al[26]	Lack of control group
Attal et al[27]	Lack of control group
Wade et al[17]	Pain reduction was not the primary outcome for all subjects and was not measured for the entire sample
Wade et al[18]	Pain reduction was not the primary outcome for all subjects and was not measured for the entire sample
Zajicek et al[28]	Pain reduction was not the primary outcome for the study and was not measured for the entire sample
Zajicek et al[29]	Pain reduction was not the primary outcome for the study and was not measured for the entire sample
Wissel et al[30]	Pain was spasticity related
Frank et al[16]	Lack of placebo control

(natural cannabinoids)[19,21,31–37,40]; 4 of these included smoked cannabis[31,32,34,35]; 5 included cannabis-based medicinal extracts (CBME) in the form of oromucosal sprays (nabiximols)[21,33,36,37,40]; and 1 utilized a novel delivery system involving vaporized cannabis.[19] The remaining 3 studies included synthetic cannabinoids, with dronabinol (a synthetic THC),[38] nabilone (an analog of dronabinol),[20] and CT-3 (1', 1'Dimethylheptyl-Δ8-tetrahydrocannabinol-11-oic acid)[39] as the active agents. The 13 studies were published between 2003 and 2013. A total of 771 subjects completed the trials. In terms of quality, the trials all rated highly on the Jadad scale, with a mean score of 4.9/5.0.

Main Outcomes

Amongst the studies utilizing whole plant cannabinoids, Abrams et al[35] found a statistically significant reduction in pain intensity in the group assigned to the active drug (3.5% smoked cannabis) when compared with placebo. In fact, daily pain decreased by 34% for active drug over placebo and a greater than 30% reduction was reported in 54% of patients taking active drug as opposed to 24% taking placebo.

Ellis et al[34] found a statistically significant decrease in pain as measured by the Descriptor Differential Scale in patients treated with cannabis compared with those treated with placebo. Participants in this trial were titrated to a target dose "affording the best achievable pain relief without unacceptable adverse effects," with the THC content of cannabis utilized ranging from 1% to 8%. The proportion of patients who obtained greater than 30% pain relief also favored those taking cannabis over those taking placebo.

Ware et al[31] compared cannabis with concentrations of 2.5%, 6%, and 9.4% THC against placebo and found a statistically significant difference in pain intensity for those using cannabis with 9.4% THC content as compared with those taking placebo.

Wilsey et al[32] noted a statistically significant decrease in both pain intensity and pain unpleasantness for those subjects taking the active agents (3.5% and 7% smoked cannabis) over those subjects taking placebo.

Wilsey et al[19] utilized a novel delivery system in their other trial which compared "medium-dose" (3.53% THC content), "low dose" (1.29% THC content), and placebo cannabis delivered in vaporized form. They showed low-dose and medium-dose cannabis to be equally effective in reducing pain intensity measured by a visual analog scale (VAS), with results that were statistically significant when compared with placebo.

Amongst the studies utilizing cannabinoid extracts, Berman et al[40] showed treatment with each of two active drugs (THC:CBD and THC alone) resulted in a statistically significant reduction in pain intensity and significant improvement in sleep when compared to treatment with placebo. The reduction in pain intensity did not meet the two-point difference (on an 11-point numerical rating scale) that was assumed by the authors on an a priori basis to be clinically significant, in accordance with Farrar et al.[41] Most (80%) of the patients enrolled in this study continued the open-label extension study utilizing the THC:CBD combination.

Like Berman et al,[40] Rog et al[37] also showed a statistically significant reduction in both mean pain intensity and sleep disturbance when the same THC:CBD extract was compared with placebo.

Nurmikko et al[36] also showed a statistically significant reduction in mean pain intensity when comparing the same extract with placebo, with more patients in the active drug group reporting greater than 30% reduction. In addition, "an open-label extension study (that included 71% of eligible subjects) showed that the initial pain relief was maintained without dose escalation or toxicity for 52 weeks."[36]

In contrast with the three aforementioned studies that investigated CBME, Selvarajah et al[33] found no

significant difference between subjects treated with THC:CBD and placebo in terms of reduction in the two primary outcome measures (mean daily pain scores and Neuropathic Pain Scale scores).

The most recent of the studies that examined CBME was that of Langford et al.[21] Of the five studies that utilized cannabinoid extracts,[21,33,36,37,40] this study was unique in that it incorporated an enriched-enrollment randomized-withdrawal design with two phases. Phase A took place over 14 weeks and was followed by phase B, which included a 14-week open-label period coupled with a 4-week randomized withdrawal period. The results were equivocal,[21] since an interim analysis showed a significant difference at week 10 of phase A in favor of THC:CBD, but at week 14 (the end of phase A) there was no statistically significant difference; the number of responders in the placebo group had increased during the final 4 weeks of phase A, while the number of responders in the active drug group remained steady. The authors speculated that the placebo response may have been related to the flexible dosing design incorporated into this and two previous studies that had utilized the oral spray. As a result, those who took placebo administered a significantly larger number of doses than those who took THC:CBD, "potentially confounding the comparison between treatment groups."[21] "When the groups were balanced for daily sprays, the THC:CBD group showed greater separation from placebo."[21] Nurmikko et al[36] and Rog et al[37] also noted that the mean number of daily sprays of CBME was significantly higher in the placebo groups of their respective studies. In phase B of the study (randomized withdrawal) by Langford et al,[21] the proportion of subjects "failing treatment" was significantly lower for those taking the CBME than for those taking placebo.

In those studies that utilized synthetic cannabinoids, Karst et al[39] showed significant pain relief when CT-3 was compared with placebo, and Svendsen et al[38] showed clinically significant improvement in pain relief reflected in reductions in spontaneous median pain intensity and radiating pain. Toth et al also noted those achieving a reduction in pain intensity greater than 30% and 50% were significantly greater, and results for sleep interference were significantly better, in the active drug group as compared to the placebo group.[20] Fewer symptoms unique to neuropathic pain sufferers as measured by the Neuropathic Pain Symptom Inventory were reported by those diagnosed with diabetic peripheral neuropathy who were taking nabilone as compared with those receiving placebo during the double-blind phase.

Adverse Events

The smoked cannabis studies reported some similarities for adverse events. Abrams et al[35] reported smoked cannabis with 3.5% THC to be "well tolerated." Ratings of adverse events were low in both active drug and placebo groups. Those events most frequently reported were sedation, anxiety, confusion, disorientation, and dizziness, and no withdrawals occurred due to adverse events.

Wilsey et al[32] also noted there were no withdrawals in their trial due to "tolerability issues." The most prominent psychoactive effects were sedation, hunger, and confusion. Extensive neuropsychological testing showed impaired cognition in those subjects taking 7% THC, while those taking 3.5% THC experienced impaired learning and memory.

Ellis et al[34] reported two subjects withdrew from their trial due to adverse events. Side effects were more frequently reported by those taking cannabis than those taking placebo; they included difficulty concentrating, fatigue, sleepiness/sedation, increase sleep duration, decreased salivation, and increased thirst.

Ware et al[31] found "no serious or unexpected adverse events" amongst those patients taking cannabis. Headache, dry eyes, burning sensation, dizziness, numbness, and cough were most frequently reported in the highest dose group (9.4% THC). Reports of "feeling high and euphoria" were very rare.

Wilsey et al[19] found subjects who took either of the active drugs to be more sedated, confused, nauseated, and hungry than those who took placebo. The side effects were dose-dependent. As in their earlier study,[32] neuropsychological testing revealed the "greatest dose effects" were "on memory and learning, where effect sizes were in the small to medium range and unlikely to have significant impact on daily functioning."

Of the five studies that utilized the cannabinoid extracts,[21,33,36,37,40] the most frequently encountered adverse effects were dizziness/vertigo, tiredness/somnolence/fatigue, dry mouth, and dysgeusia. An increased incidence of mouth ulcers, dysgeusia, and sore throat was associated with the use of the oromucosal spray, a cannabinoid extract combined with ethanol.[21,37,40] Rog et al[37] reported "cognitive side effects were limited to long-term memory storage" and Nurmikko et al[36] found no variation in "objective measurement of psychomotor performance" between the active drug and placebo groups.

Adverse effects of dizziness, tiredness, headache, and myalgia were most frequently encountered in the subjects who received dronabinol.[38] In those who received nabilone for treatment of diabetic peripheral neuropathy, confusion was the most serious among a number of adverse effects, which were generally "mild to moderate in intensity" and which also included "dizziness, dry mouth, drowsiness, impaired memory, lethargy, euphoria, headache, and increased appetite."[20]

Finally, in subjects who received the synthetic cannabinoid CT-3, tiredness and dry mouth were reported as the most frequent adverse effects, but no major physical adverse effects were observed.[39]

Duration of the Treatment

The duration of the treatment of the selected studies ranged from less than 1 week to 6 weeks or more. This variability did not appear to have affected the primary outcome of the studies.

Number Needed to Treat (NNT)

Nine out of 13 studies clearly stated a NNT ranging from 2 to 4, with no differences among type of cannabinoids. A simple calculation of the reciprocal of results difference between active treatment and placebo allowed the authors to assess that the sample size was adequate for all the remaining four papers, except for that of Selvarajah et al.[33]

Discussion

The quasi-totality of the high-quality studies included in the present systematic review suggests that cannabinoids provide significant pain reduction in both the short term and longer term, without significant side effects, but must be balanced with the equivocal results of one very large study[21] and with a number of negative unpublished trials (http://www.clinicaltrials.gov/ct2/results?term=cannabis+neuropathic+pain). In the only published study[33] with negative results, it was noted that depression (as measured by the depression subscale of the Hospital Anxiety and Depression Scale) was a major confounder. However, there were other significant limitations apparent in its design. It was stated by the authors that "there was a significant main effect of depression on total pain score (TPS), suggesting that in both treatment arms, patients who were depressed were more likely to respond to intervention."[33] TPS was defined by the authors as the "average score of all three pain modalities," which are described as "superficial, deep, and muscular pain."[33] However, none of these three pain modalities was specifically defined by the authors, the association between each of the three modalities and diabetic peripheral neuropathy was not explained, and nowhere in the article was TPS supported as a valid measure for painful diabetic peripheral neuropathy. Although subjects were screened for depression, it was not specified if they were screened for other psychiatric disorders, nor was it specified, in the case of those subjects who were considered depressed, if the depression was associated with their underlying condition. The authors did not provide a summary of the specific classes/names of concomitant medications taken by subjects who participated in the study. Instead, they simply indicated: "Patients continued preexisting neuropathic pain treatment during the study" and "those with persistent pain, despite an adequate trial of tricyclic antidepressants, were recruited."[33] In addition, the study was a parallel group design that included a total of only 29 subjects randomized to two arms, and there was no indication of the NNT and no evidence provided to support the adequacy of the study sample size.[33]

A more recent systematic review and meta-analysis[14] that examined cannabis treatment for chronic pain concluded, "currently available evidence indicates that treatment of chronic pain based on cannabinoids compounds would entail more risk than benefit, including the risk of the appearance of events in which the pain—if it is of low intensity—might even come to pose a secondary problem in the subject." In contrast, the present systematic review found very few risks related to the use of cannabinoid compounds in the treatment of chronic neuropathic pain. The vast majority of adverse events listed were considered minor in nature. As well, open-label extensions up to 2 years in duration failed to reveal any evidence of longer-term side effects.

Many of the cannabinoid studies evaluated in the present systematic review indicated that the medications traditionally used to treat chronic pain (such as opioids and anti-epileptic drugs) are of limited therapeutic value in managing chronic neuropathic pain and also have adverse effects. Most of these studies added cannabinoids to a stable regimen of patients' current medications. Many of these patients reported intractable pain of higher intensity. Hence, cannabinoids should be considered at least an effective adjunct if not an alternative therapy for the treatment of chronic neuropathic pain. But of note in this regard was the observation in one study[37] that the meta-analysis upon which Farrar et al[41] based the suggestion that a 30% reduction in pain was clinically significant "did not include patients with central neuropathic pain, in which relatively small decreases in pain intensity are often highly valued by patients."

A limitation of the present systematic review was the variability in duration of the studies evaluated. Although the authors did not find any evidence for an effect of treatment duration, probably due to the chronic nature of neuropathic pain conditions evaluated, this variability may play a potential role in the results of the studies and must be taken into account in evaluating these results. The systematic review also did not address the differences in efficacy or adverse effects among the different types of cannabinoids and the methods of their administration. In addition, although it covered several chronic nonmalignant

neuropathic pain conditions, a consistent feature was the significant improvement of pain across the studies.

Newer delivery methods for cannabinoids are much safer than smoking. Oromucosal spray systems provide more consistent blood levels and thereby allow titration to effective levels of analgesia while minimizing adverse effects. The oromucosal delivery systems also provide a level of abuse protection by limiting the number of daily applications.

Other benefits of cannabinoids appear to include improvement in sleep quality, appetite, nausea, and anxiety. Recently developed synthetic cannabinoids, such as CT-3, await further testing in order to determine their effectiveness in various chronic pain situations and to compare their side effect profiles with traditional synthetic cannabinoids, such as dronabinol and nabilone, as well as along with newer cannabinoid extracts.

Conclusions

This systematic review suggests that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments. Further high-quality studies are urgently needed to assess the impact of the duration of the treatment as well as the best form of drug delivery.

Acknowledgments

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