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Cannabinoids for Pain Management in Patients with Neuropathic Pain: An Evidence-Based Educational Module

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Cannabinoids for Pain Management in Patients with Neuropathic Pain: An Evidence-Based Educational Module

A DNP Project Presented to the Faculty of the
Nicole Wertheim College of Nursing and Health Sciences

Florida International University


In partial fulfillment of the requirements
For the Degree of Doctor of Nursing Practice

By

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Abstract

Background: Neuropathic pain is one of the more difficult diseases to treat due to the challenges with both diagnosis and definitive pharmacological interventions.¹ Many patients with neuropathic pain are unsatisfied with their pain control due to either shortcomings with the effectiveness of their medications (gabapentin, pregabalin), or inability to withstand the side effects that are common with these drugs.^{1,4,6} Cannabinoids present a potential solution to individuals that don't tolerate other medications and with its recent legality across the United States, more and more research is being conducted supporting its efficacy in pain management of a variety of diseases.

Methods: A quality improvement project was conducted to review the efficacy of cannabinoid administration in individuals with inadequate pain control secondary to neuropathic pain. With this information, an online educational module was constructed and disseminated to practicing anesthesia providers. There was a pretest and a post-test to assess the degree of learning that took place and any shifts in attitude. This educational module was developed through an anesthesia company and utilized an anonymous, online platform for delivery and data collection.

Results: After the educational module was presented to participating anesthesia providers, the participants showed an increased in knowledge about both neuropathic pain and cannabinoid administration. The participants also showed an improved perception about the administration of cannabinoids to patients with neuropathic pain.

Discussion: Anesthesia providers seem to be somewhat hesitant to utilize cannabinoids for their patients. This seems to be due to lack of knowledge on cannabinoids and its safety profile. Through the education module, the information presented on its benefits and risks seemed to shift the attitude of the participating anesthesia providers. While the sample size was small and one cannot generalize the results of the educational module to all anesthesia providers, there is potential to educate anesthesia providers and produce a shift in perception on the efficacy and safety of cannabinoid administration in those suffering from neuropathic pain.

Key Words: Neuropathic Pain, Cannabinoids, Pain Management, Medical Marijuana, Gabapentin, Education

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Introduction

Neuropathic pain (NPP) is one of the more difficult diseases to treat as evidenced by the lack of adequate pain relief reported by patients that are commonly on multi-modal therapies. NPP often develops secondary to a disease or lesion that affects the somatosensory pathways in the peripheral or central nervous systems. Some common diseases associated with NPP are Diabetes Mellitus (DM), radiculopathy, spinal cord injuries, strokes, and Multiple Sclerosis (MS).¹ There may be additional causes of NPP such as chemotherapy, nerve damage secondary to either trauma or surgery, or NPP can be idiopathic in nature.² One of the many problems associated with NPP is the fact that there is no definitive diagnostic testing leading to untreated pain and unsatisfied patients.¹ While this disease process has been challenging to treat and is without a gold standard diagnostic test, it is estimated that up to 10% of the general population can be suffering from NPP. In the United States, it is estimated that about 30 million individuals have a diagnosis of DM; out of the 30 million, about 10 million also have diabetic peripheral neuropathy.³ Additionally, it is estimated that between 25% and 46% of peripheral neuropathy cases are idiopathic in nature.² Treatment of the underlying disease is often necessary to prevent the NPP from worsening, but that is hard to do when the cause of the NPP is not detectable. In addition to the difficulties of treating the underlying diseases, NPP is often refractory to medical management with many of the above patients reporting inadequate pain control on their current regimens.⁴ As one can imagine, with millions suffering from NPP and a lack of a definitive treatment, there is a significant number of individuals that are living with insufficient medical therapy which undoubtedly affects their day-to-day lives.

There are a plethora of treatments for NPP, both pharmacological and non-pharmacological. While non-pharmacological is desired in most pain management scenarios

because of the side effects associated with many of the medications, NPP is unique in that it's sporadic and does not need to have a nerve impulse to elicit pain.¹ This essentially means that it is difficult for these patients to avoid activities that induce the pain because of neuropathy's irregular, uncontrollable nature. This leads to the mainstay of attempted treatments being pharmacological in nature. NPP is often refractory to the usual methods such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs).⁵ The primary medications utilized by these patients are gabapentin and pregabalin. Both of these medications have been shown to be beneficial to patients based on pain scores and sleep scores. However, the shortcomings of these drugs are the unfortunate side effects such as: somnolence, weight gain, edema, fatigue, vertigo, and many other symptoms. This often leads to patients discontinuing the medication leading to them just dealing with the pain and the consequences of untreated NPP as stated above.⁶ The proposed solution is the addition of cannabis-based medications to treatment regimens. There are an abundance of studies supporting the use of cannabis-based medicines to treat NPP as it has been shown to have effective analgesic effects in those refractory to other treatments.⁷ There are side effects associated with cannabis, as with any other medication, but cannabis-based method is an avenue of pharmacological treatment that should be explored for this patient population to ensure that everything that can be done to try to combat this condition is taking place.

Background

Neuropathic pain can be defined as a hypersensitivity to an abnormal stimuli and a nociceptive response related to non-noxious stimuli. The problem with this type of pain is that it's very hard to control and current treatments only have moderate effectiveness while causing a plethora of side effects.⁸ Gabapentin is a commonly used medication for patients with neuropathy. Many studies show that gabapentin's effectiveness is limited. Specifically, it has

been shown that over half of those treated with gabapentin will not achieve their desired level of pain relief but will still have a high possibility of experiencing its adverse events, such as dizziness, gait disturbance, peripheral edema, and somnolence.⁹ Although Cannabis has grown in popularity in the United States, it is still a relatively experimental drug. But with the recent medicinal legalization in many states, research has exploded, with pain management being a primary goal of many research articles. Pain management is one of the many responsibilities taken on by anesthesia providers. Individuals with NPP continually struggle with pain management. However, that does not need to be the case; there is an abundance of research supporting the use of cannabinoids to improve the pain scores in individuals with NPP. The next step is to incorporate the use of cannabinoids into the pain management regimen for individuals with NPP. While neuropathic pain is often viewed as an outpatient issue, it can also affect patients getting surgery and an increase in pain medication requirements perioperatively. Many Enhanced Recovery After Surgery (ERAS) protocols include administration of gabapentin preoperatively. This is something that can be improved upon as gabapentin often takes days to have any affect, so a one-time administration before surgery really isn't doing much for the patient. Given the side effect profile of gabapentin as mentioned above, some patients may not benefit from multiple doses of gabapentin and cannabis-containing medications may be more tolerable and elicit the same or improved therapeutic effects.

As previously stated, the hindrance of a lack of definitive medical regimen for the treatment of NPP is a significant problem in this patient population. Due to there being no cure for the disease, this leads to these individuals having to cope with NPP for the rest of their lives; therefore, strides towards an effective treatment must continue to be pursued. While NPP is

often caused by other diseases, NPP itself can lead to more comorbidities. NPP can turn into chronic pain and is associated with sleep disorders, depression, and drug dependency.⁵

Summary of the Literature

As previously stated, the treatment of neuropathic pain can be difficult to accomplish and must be catered to the individual patient. While gabapentin and pregabalin are staples in the treatment for NPP, these medications are not always tolerated or effective in treating the pain.⁶ The articles selected for this literature review focus on the use of cannabinoids in various forms and their effects on pain scores and other various evaluation methods in those suffering from NPP. There are also various types of neuropathic pain, including diabetic, Multiple Sclerosis (MS)-induced, chemotherapy-induced, general peripheral neuropathy, and various others. There are similarities to problems associated with gabapentin and other pharmacological interventions, such as, discontinuation of the drug because of the associated side effects. However, the majority of the articles selected concluded that cannabinoids do decrease the pain levels in some of the individuals in the studies, but a definitive statement that it should be a mainstay in treatment cannot be made based on the results of the studies.¹⁰⁻¹⁷ More research must be done to solidify the use of cannabinoids in the NPP patient population to help with their pain management. The overall safety of cannabinoids seems to be benign; but again, more long-term studies must be done to draw these conclusions definitively.¹⁶ While the evidence isn't definitive at the moment, the use of cannabinoids in its various forms should be tried in those suffering from NPP without adequate pain relief because an individual may not get pain relief from gabapentin (or other medications) but it's possible they may get pain relief from cannabinoids. Additionally, if a patient is not tolerating the side effects from other pharmacological treatments,

they may tolerate the side effects from cannabinoids. The treatment of these patients must be individualized, and this is an avenue that should be explored.

PICO

Population (P): Anesthesia providers involved in pain management

Intervention (I): Prescribing cannabinoids to patients with NPP who have uncontrolled pain

Comparison (C): None

Outcomes (O): Improved pain scores and outcomes for these patients with NPP

Methodology for Literature Review

A literature search was carried out using the PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and MEDLINE databases. The keywords utilized to complete the searches were (cannabis or marijuana or THC or CHD or tetrahydrocannabinol or cannabinoid) and (neuropathy or peripheral neuropathy or neuropathic pain). The filters applied to the search were: dates (2014-present), type of article (clinical trial, Randomized Control Trial (RCT), and systematic reviews), and full text availability. Utilizing these filters and keywords, a total of 121 articles were found meeting the criteria throughout the three databases. After meticulously reviewing the abstracts for these articles, ten of the articles were selected to be reviewed to assess the successful, or unsuccessful usage of cannabinoids to combat neuropathic pain. A total of 5,536 patients participated in the ten studies chosen to be reviewed.

Literature Review

As stated previously throughout this paper, there is an abundance of evidence that supports cannabinoid use in treating patients with NPP. Although many of the studies focus on pain scores, some of the studies evaluate more intricate values that help provide more subjective and objective data on the success of cannabinoid administration to these patients. Weizman et

al¹⁰ performed a Randomized Control Trial (RCT) that characterized the functional brain changes in conjunction with δ -9-tetrahydrocannabinol (THC) modulation of NPP. The study was a double-blind, placebo-controlled trial that used a counterbalanced, within-subjects design. A total of fifteen patients with chronic radicular neuropathic pain participated and underwent pain assessments and functional resting-state brain scans both at baseline and after sublingual THC administration. The study then examined the functional connectivity of the anterior cingulate cortex and its pain-related dynamics using graph theory measures.¹⁰

The results of this study found that THC significantly reduced the patients' pain scores when compared to the placebo group. This THC-induced analgesia was concurrent with a reduction in functional connectivity between the anterior cingulate cortex and the sensorimotor cortex. This reduction was predictive of the response to the THC and graph theory analyses of local measures demonstrated a reduction in network connectivity in areas involved in pain processing (specifically in the dorsolateral prefrontal cortex), which are linked with individual pain reduction. These results lead the researchers to believe that 2 major cognitive-emotional modulation areas, the anterior cingulate cortex and dorsolateral prefrontal cortex, and their connections to the somatosensory areas, are functionally involved in the analgesic effect of THC in chronic pain. Therefore, this effect may be mediated through the induction of functional disconnection between regulatory high-order affective regions and the sensorimotor cortex. Assessing a baseline functional connectivity between these brain areas may help predict the extent of pain relief induced by THC.¹⁰

Lynch et al¹⁸ also performed an RCT utilizing a double-blind, placebo-controlled, crossover pilot trial. This study took an in-depth look at neuropathic pain caused by chemotherapy limited dosing and the duration of potentially life-saving anti-cancer treatment and

its impact on quality of life. While all NPP can be difficult to treat, chemotherapy-induced NPP is notorious for responding poorly to conventional treatment methods. With a few preclinical studies showing suppression of established chemotherapy-induced neuropathy using cannabinoid agonists, there was hope that this RCT would yield positive results. This pilot trial began to investigate a currently available cannabinoid agent, nabiximols (oral mucosal spray) in patients with chemotherapy-induced NPP. A randomized, placebo-controlled crossover pilot study with 16 patients with the aforementioned chemotherapy-induced NPP was performed. The primary outcome measure was a 0–10-point numeric rating scale for pain intensity.¹⁸

Unfortunately, the results of this study did not yield the positive results indicated by the pretrials. There was no statistical difference between the treatment and placebo groups in pain intensity. The study did show that five participants reported a two-point or greater reduction in pain that was trending toward statistical significance, but it did not reach that goal. Going into the study, chemotherapy-induced NPP was known to be difficult to treat and this study confirmed this. While the statistical significance threshold was not reached, this study did provide hope that further advancements in cannabinoids could affect more participants positively. The researchers concluded that additional studies on nabiximols in fully randomized, placebo-controlled trials in the chemotherapy-induced NPP population should be explored.¹⁸

Another RCT was performed by Turcotte et al¹¹ that assessed the administration of Nabilone, an oral pill, as an adjunct to gabapentin. This study is unique in the fact that the researchers were attempting to add a cannabinoid to a medication regimen including the most popular NPP medicinal treatment option. Turcotte et al¹¹ utilized participants with Multiple Sclerosis (MS) induced NPP, for which there is no cure. This disease is also difficult to treat due to the underlying multifaceted pathogenesis. This study used a randomized, double-blind,

placebo-controlled trial involving fifteen relapsing-remitting MS patients who were already prescribed gabapentin. To be eligible, the patients had to be stabilized on a gabapentin dose of at least 1,800 mg and still have inadequate pain relief. The participants were then treated with either Nabilone or a placebo. The Nabilone was titrated over 4 weeks (0.5 mg/week increase) followed by a 5-week maintenance of 1 mg oral Nabilone (or placebo) twice a day. The outcome measures were a twice-a-day visual analog scale determining pain intensity and the impact of pain on daily activities. There was a hierarchical regression model conducted on each outcome to determine the pain trajectory across study groups during the 63-day follow-up.¹¹

The results of the study showed that a significant group interaction term was reported for both the pain intensity and pain impact visual analog scores. The adjusted rate of decrease for both outcomes was statistically greater in the nabilone group compared to the placebo study group. There was not a significant difference in attrition rates between the two treatments showing that nabilone was well tolerated (dizziness/drowsiness was the most frequently reported adverse effect). This data allowed the researchers to conclude that nabilone as an adjunct to gabapentin is an effective, well-tolerated combination for patients suffering from MS-induced NPP. This combination of medications is a potential therapeutic regimen for a patient population that is predisposed to tolerability issues and may lead to effective pain management in the future.¹¹

Mücke et al¹² performed a systematic review focusing on cannabinoids and their effects on patients with chronic NPP. The review found that 6-10% of chronic pain syndromes have a neuropathic component and current pharmacological treatment options for this subtype show the perceived benefits to be outweighed by the adverse effects. The review's goals were to assess the efficacy, tolerability, and safety of cannabinoids compared to placebo or conventional drugs for

conditions deemed to be chronic NPP. This review was conducted in 2017 using CENTRAL, MEDLINE, Embase, and two trial registries for published and ongoing trials, while also reviewing the reference lists for these articles. The authors selected randomized, double-blind control trials of medical cannabis, plant-derived, and synthetic cannabis-based medicines pitted against a placebo or any other active treatment. The treatment duration must have been at least two weeks and at least ten participants per treatment. Three review authors extracted the data independently and looked at study characteristics and outcomes of efficacy, tolerability, and safety. For efficacy, they calculated the number needed to treat additional beneficial outcomes for pain relief of 30% and 50% or greater. The authors also looked at dropout rates due to lack of efficacy and standardized mean differences for pain intensity, sleep problems, health-related quality of control, and psychological distress. For tolerability, the authors calculated the number needed to treat additional harmful outcomes for withdrawal due to adverse events and specific adverse events, nervous system disorders, and psychiatric disorders. The quality of evidence was assessed using GRADE and then a 'Summary of Findings' table to was created.¹²

There were 16 studies with 1,750 participants analyzed in this review. The studies ranged from 2 to 26 weeks long and compared oromucosal spray with THC and cannabinoids (10 studies), a synthetic cannabinoid, nabilone (2 studies), inhaled cannabis (2 studies), and plant-derived THC, dronabinol (2 studies). Fifteen of the studies were compared against a placebo, and one was compared against an analgesic, dihydrocodeine. Study qualities ranged from low (2 studies), moderate (12 studies), and high (2 studies). Cannabis-based medicines were shown to potentially increase the number of people achieving 50% or greater pain relief by 21% versus 17% in the placebo group. There was a 10% withdrawal rate from the cannabis-based groups due to adverse effects compared to 5% from the placebo group. For participants

achieving 30% or greater pain relief, there was a rate of 39% for those administered cannabinoids and 33% for those administered a placebo. Nervous system adverse events were 61% with cannabinoids versus 29% with placebo, but this was deemed low-quality evidence by the authors. There was no evidence of long-term risks in the studies analyzed and neither the cannabinoid group nor the placebo group differed substantially in tolerability. The authors concluded that the potential benefits of cannabis-based medicine in chronic NPP patients may be outweighed by their potential harms.¹²

Andreae et al¹³ performed a meta-analysis of individual patient data on inhaled cannabis for patients with chronic NPP. There is evidence that inhaled cannabis may alleviate chronic NPP, so the authors' objective was to synthesize the evidence on its use. They performed a systematic review and meta-analysis of individual patient data by searching Cochrane Central, PubMed, EMBASE, and AMED. They considered all RCTs investigating chronic painful neuropathy and comparing inhaled cannabis with a placebo. The treatment effects were then pooled following a hierarchical random-effects Bayesian responder model for the population-averaged subject-specific effect. Their evidence synthesis included individual data from 178 participants with 405 observed responses in 5 RCTs following patients for days to weeks providing evidence of the effects of inhaled cannabis.¹³

The results showed a short-term reduction in chronic NPP for 1 in every 5 to 6 patients treated with a Bayesian 95% credible interval. The authors cautioned that due to the small number of studies and participants, the short follow-up, shortcomings in allocation concealment, and considerable attrition limit the conclusions that can be drawn from the review. The authors concluded that there must be pragmatic trials to evaluate the long-term risks and benefits of cannabinoid administration to patients with NPP.¹³

Another systematic review was conducted by Nugent et al.¹⁹ This review focused on the effects of cannabis on those with chronic pain and an overview of the general harms of cannabinoid administration. With cannabinoid's recent legalization, the drug is becoming increasingly available for chronic pain treatment; however, its efficacy cannot be stated as certain. This review utilized MEDLINE, the Cochrane Database of Systematic Reviews, and several other sources from the database's inception until March of 2017. The studies selected for the review were intervention trials and observational studies involving adults using plant-based cannabis preparations that reported pain, quality of life, or adverse effect outcomes. Two primary investigators independently abstracted study characteristics and assessed study quality, and the investigator group graded the overall strength of evidence using standard criteria.¹⁹

There was a total of 27 chronic pain trials used for this systematic review. There was low-strength evidence that cannabis helped reduce pain scores in patients with NPP specifically, but insufficient evidence in other pain populations. Assessing 11 systematic reviews and 32 primary studies, the authors found that the harms to the general population included an increase in motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment. There were no adverse pulmonary effects seen in younger populations; however, evidence on long-term physical harms in heavy or long-term cannabis users, or older populations, is lacking. The limitations stated by the authors were the lack of methodologically rigorous trials and that the cannabis formulations studied may not be available commercially for consumption by the general public. The authors concluded that there is limited evidence suggesting that cannabis may alleviate NPP, but insufficient evidence for other chronic pain syndromes.¹⁹

Wallace et al¹⁴ performed an RCT that focused on patients with diabetic neuropathy and inhaled cannabinoids. The researchers used a randomized, double-blinded, placebo-controlled

crossover study with 16 patients diagnosed with diabetic peripheral neuropathy. The objective of the study was to assess the short-term efficacy and tolerability of inhaled cannabis. Using a crossover design, each participant was exposed to 4 single-dosing sessions of a placebo, or low, medium, or high doses of THC (1%, 4%, and 7% respectively). The patients reported baseline scores of spontaneous pain and evoked pain, and cognitive testing was performed. The participants were then administered aerosolized cannabis or placebo and pain intensity and subjective "highness" scores were measured at 5, 15, 30, 45, and 60 minutes, and then every 30 minutes for an additional 3 hours (total of 4 hours). The primary analysis then compared the differences in spontaneous pain scores over time between doses using a linear mixed effect model.¹⁴

There was a significant difference in spontaneous pain scores between doses. There was a dose-dependent reduction in spontaneous pain scores over time and there was a significant effect of the high dose on foam brush and von Frey evoked pain. There was also a significant negative effect with impaired performance on 2 of the 3 neuropsychological tests in the individuals that received the high dose. The researchers concluded that this RCT added to the preliminary evidence to support further research on the efficacy of cannabinoids in patients suffering from various NPP syndromes.¹⁴

There's another systematic review with meta-analysis constructed by Sainsbury et al.¹⁵ This review focused on the efficacy of cannabis-based medications compared to placebos for treatment of chronic NPP. Due to NPP presenting so many therapeutic challenges and the interest in cannabis-based medications outpacing the knowledge of its efficacy and safety, the objective of the review was to evaluate cannabinoid effectiveness in individuals with NPP. The authors utilized randomized placebo-controlled trials using THC, cannabidiol (CBD),

cannabidiol (CBD), or synthetic cannabinoids for NPP treatment. The databases used were MEDLINE, Cochrane Library, EMBASE, and Web of Science. The primary outcome was NPP intensity, and the risk of bias analysis was based on the Cochrane Handbook.¹⁵

The search provided 379 records with 17 RCTs available that met the criteria. The RCTs combined had a total of 861 patients. Using meta-analysis, the authors showed that there was a significant reduction in pain intensity for THC/CBD by -6.624 units, THC by -8.681 units, and dronabinol by -6.0 units when compared to a placebo on a 0-100 scale. CBD and CBDV showed no significant differences. The THC/CBD group was 1.756 times more likely to achieve a 30% reduction in pain and 1.422 times more likely to achieve a 50% reduction in pain when compared to the placebo groups. Patients in the THC group had a 21% higher improvement in pain intensity and were 1.855 times more likely to achieve a 30% reduction in pain than the placebo group. The authors concluded that while THC and THC/CBD interventions provided significant improvements in pain intensity, the evidence was of moderate-to-low quality. Further research is needed for CBD, dronabinol, and CBDV.¹⁵

Cannabinoids can be deemed a potential treatment option for patients suffering from NPP with the support of the articles discussed above. The main limitation that is stated in almost every article discussed is the inability to generalize this information due to the lack of a substantial number of supporting articles. Cannabinoids are rapidly gaining legalization; however, due to their illegality until recently, long-term studies have not been feasible. With more states in the United States allowing this medication to be used medicinally, and recreationally, the number of research studies into cannabinoid administration should continue to rise. Regardless of the inability to generalize these findings, it's encouraging the majority of studies found that cannabinoid administration improved pain scores in some capacity, even if

low-level evidence was the culprit. The vast majority of these studies also showed participants tolerating the intervention with limited, or tolerable, adverse effects.

The following matrix provides a more in-depth review of the ten articles utilized to review the literature on the topic of cannabinoids and their administration in patients with various forms of NPP.

Citation	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/ Level
Weizman et al, ¹⁰ 2018	<p>RCT Purpose: effect of THC on pain scores and brain activity in individuals with chronic neuropathic pain</p> <ul style="list-style-type: none"> Administer THC and placebo, then evaluate change in pain scores and brain scan utilizing fMRI 	<p>15 participants with chronic lumbar radicular pain, all male</p> <p>Attrition Rate: NR</p> <p>Setting: one in 2 different meetings in a clinical setting</p>	<p>Independent Variables: THC</p> <p>Dependent Variables: fMRI results (functional connectivity between anterior cingulate cortex and sensorimotor cortex) and pain scores</p>	<p>fMRI: graph theory analysis looking at the somatosensory cortex</p> <p>Pain scores: VAS score before and after treatment</p> <p>Statistical analysis done using STATISTICA 10 software for pain scores and Statistical Parametric Mapping software for fMRI</p>	<p>Pain scores: THC post-pre = 18.8 ± 5.6, placebo post-pre = 8.7 ± 5.5</p> <p>Three clusters within the sensorimotor cortex were found: the right and left secondary somatosensory cortex and the right motor cortex (right SII [areas OP4, OP1: MNI coordinates 64, -16, 20; 121 voxels, T(13) = 8.92, cluster p-FDR = 0.0023]; left SII [areas OP4, OP1: MNI coordinates 66, -20, 22; 67 voxels, T(13) = 7.77, cluster p-FDR = 0.0286]; and right MI [area 4a: MNI coordinates 30, -16, 64; 95 voxels, T(13) =</p>	<p>THC significantly reduced the subjective perceived ongoing pain rated with the VAS score prior to and immediately after fMRI scanning.</p> <p>THC-induced analgesia was correlated with a reduction in functional connectivity between the anterior cingulate cortex and the sensorimotor cortex.</p>	<p>Two of the major cognitive-emotional modulation areas and their connections to somatosensory areas were directly involved in the effects of THC on chronic pain. These findings coupled with decreases in VAS pain scores may serve as a predictor to the extent of pain relief secondary to THC administration.</p>	<p>Level of Evidence: II</p> <p>Strengths: innovative way to interpret pain (fMRI), unbiased results of pain scores, promising results post-THC administration</p> <p>Weaknesses: females excluded from study, small scale study, variability of cannabinoids in THC, different patient demographics needed</p> <p>Feasibility: Additional, larger-scale research</p>

					7.22, cluster p-FDR = 0.0081]. The MNI coordinates of local maxima for each region are reported)			must be completed before this can become common practice. Use of fMRI to assess pain reductions may not be feasible as the technology is expensive. Utilizing THC as an adjunct to chronic NPP management is obtainable.
Lynch et al, ¹⁸ 2014	<p>RCT Purpose: effect of oral mucosal cannabinoid on pain scores in individuals with chemotherapy-induced neuropathic pain</p> <ul style="list-style-type: none"> Administer mucosal cannabinoid and placebo, then evaluate pain scores 	<p>18 participants with established chemotherapy-induced neuropathy</p> <p>Attrition Rate: 2 patients (reason not stated)</p> <p>Setting: study completed over 4 weeks in a combined clinical and home setting</p>	<p>Independent Variables: Oral mucosal cannabinoid extract</p> <p>Dependent Variables: Pain scores, adverse events</p>	<p>Pain scores: NRS-PI</p> <p>Adverse events: Short form-36 Health Survey</p> <p>Statistical analysis done with ANOVA</p>	<p>The mean pre-treatment (seven-day average) NRS-PI score was 6.75 (6.17-7.33). During active treatment, the mean NRS-PI score dropped to 5.5 (4.43-6.57) at mid-treatment (during placebo treatment: 6.31 [5.58-7.04]) and to 6.00</p>	<p>No statistically significant difference between the treatment and the placebo groups on the NRS-PI</p>	<p>Chemotherapy-induced neuropathy continues to be challenging to treat</p> <p>Statistics don't show a significant difference, but individuals claiming improvement leads the authors to</p>	<p>Level of Evidence: II</p> <p>Strengths: Unbiased results, strong method of evaluation using NRS-PI, unique patient population</p> <p>Weaknesses: Inconclusive results, more studies</p>

	using numeric pain rating scale				(6.98-5.02) at the end of four weeks of active treatment (placebo treatment: 6.38 [5.67-7.09]). A repeated measures ANOVA demonstrated that, for 16 participants who completed the study, there was a main effect for time (P=0.007) but not for the interaction of time and treatment condition (P=0.29) or for the between-subjects factor (P=0.52). Analysis of SF-36 and QST demonstrated no statistically significant effect as compared with placebo		support future RCT with nabiximols	needed at a larger scale Feasibility: Using CBD in a patient population that has trouble controlling pain is warranted and should continue to be researched. Implementation into practice is obtainable.
Turcotte et al, ¹¹ 2015	RCT Purpose: effect of nabilone (cannabinoid)	15 participants with MS-induced NPP on a stabilized	Independent Variables: Nabilone	Pain score: VAS pain	Statistically significant group by time interaction terms	A significant group to time interaction term was	Nabilone as an adjunctive to gabapentin	Level of Evidence: II

	<p>with gabapentin on pain scores in individuals with multiple sclerosis-induced neuropathic pain</p> <ul style="list-style-type: none"> • Administered nabilone and a placebo to individuals on a therapeutic regimen of gabapentin, then evaluated pain scores 	<p>dose of gabapentin with inadequate pain relief</p> <p>Attrition Rate: 1 patient (reason not stated)</p> <p>Setting: study done in a combined clinical and home setting over 9 weeks</p>	<p>Dependent Variables: Pain score, impression of change, adverse events</p>	<p>Impression of change: VAS impact</p> <p>Adverse events: Adverse event checklist</p> <p>Analyzed using independent t-tests, chi-squared tests, and R Software</p>	<p>for each of VAS pain ($P < 0.01$) and VAS impact ($P < 0.01$) study outcomes. For both outcomes, trajectories of pain deviated significantly from a linear trend and hence second-order time measures were included in the interaction term.</p> <p>Demonstrates that the rate of loss (i.e., reduction) in VAS pain intensity was greater, on average, in the nabilone vs placebo study group. This significant difference was maintained during both the titration and maintenance phases of the follow-up period. Conversely, the rate of reduction in VAS impact was greater on</p>	<p>reported for both pain and impact scores showing that the adjusted rate of decrease for both was significant for nabilone versus the placebo group. No significance in difference for attrition rates showing that Nabilone was tolerated well</p>	<p>is an effective, well-tolerated combination for MS-induced NPP.</p>	<p>Strengths: Able to evaluate Nabilone with gabapentin, another common treatment for NPP. Unbiased results. Assessed efficacy using multiple VAS scales.</p> <p>Weaknesses: Small sample size, assessed a specific patient population that may not be able to generalize to most patients with NPP.</p> <p>Feasibility: Promising results which warrant future research, implementin</p>
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					<p>average for the placebo group during the titration phase of the follow-up period only.</p> <p>Of the nabilone study group, 100% of respondents noted an improvement in their condition (responses 1–3 on rating scale), whereas only 43% of the placebo group documented any improvement.</p> <p>The most commonly reported side effects among the nabilone/GBP-treated patients were dizziness (62.5%) followed by drowsiness and dry mouth (50%)</p>			g Nabilone into treatment regimens in those with MS-induced NPP is obtainable.
Mücke et al, ¹² 2018	SR Purpose: effect of cannabinoids on pain relief in individuals with chronic	16 studies with 1,750 participants ranging from 2-26 weeks long	Independent Variables: medical cannabis, plant-derived and synthetic	Pain relief: VAS and SRI Adverse events: checklist	Cannabis-based medicines may increase the number of people achieving 50% or greater	All cannabis-based medicines pooled together were better than	The potential benefits of cannabis-based medicine	Level of Evidence: I Strengths: Large sample size

	<p>neuropathic pain</p> <ul style="list-style-type: none"> Searched 5 databases from 1946 to 2017 Selected only randomized, double-blind control trials using medical cannabis, plant-derived and synthetic cannabis-based medicines compared with a placebo Treatment had to have a duration of at least 2 weeks and at least 10 participants 	<p>Attrition Rate: 10.4% in cannabis-based medicine group and 4.7% in placebo group based on adverse events</p> <p>Setting: United Kingdom, Canada, United States, Germany, Denmark, multiple other European Countries</p>	<p>cannabis-based medicines</p> <p>Dependent Variables: reported pain relief, adverse events</p>	<p>Analysis utilized GRADEpro Guideline Development Tool Software</p>	<p>pain relief compared with placebo (21% versus 17%; risk difference (RD) 0.05 (95% confidence interval (CI) 0.00 to 0.09); NNTB 20 (95% CI 11 to 100); 1001 participants, eight studies, low quality evidence). We rated the evidence for improvement in Patient Global Impression of Change (PGIC) with cannabis to be of very low quality (26% versus 21%; RD 0.09 (95% CI 0.01 to 0.17); NNTB 11 (95% CI 6 to 100); 1092 participants, six studies). More participants withdrew from the studies due to adverse events with cannabis-based medicines (10% of participants) than</p>	<p>placebo for the outcomes substantial and moderate pain relief and global improvement. All cannabis-based medicines pooled together were better than placebo in reducing pain intensity, sleep problems and psychological distress.</p> <p>There was no difference between all cannabis-based medicines pooled together and placebo in improving health-related quality of life, stopping the medication because it was not effective, and in the frequency of serious side effects</p>	<p>(herbal cannabis, plant-derived or synthetic THC, THC/CBD Oro mucosal spray) in chronic neuropathic pain might be outweighed by their potential harms. The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities from the studies, together with their small sample sizes.</p>	<p>with 16 studies and 1,750 participants, comparison across studies, strict criteria for inclusion into study</p> <p>Weaknesses: mainly low-quality evidence analyzed per the authors, failure of most studies included to have adequate exclusion criteria for participants, cannot generalize findings to rest of patient population</p> <p>Feasibility: Implementing CBD into NPP management regimens is obtainable.</p>
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					with placebo (5% of participants) (RD 0.04 (95% CI 0.02 to 0.07); NNTH 25 (95% CI 16 to 50); 1848 participants, 13 studies, moderate-quality evidence). The authors did not have enough evidence to determine if cannabis-based medicines increase the frequency of serious adverse events compared with placebo (RD 0.01 (95% CI -0.01 to 0.03); 1876 participants, 13 studies, low-quality evidence).			
Andreae et al, ¹³ 2015	SR and MA Purpose: effects of inhaled cannabis on pain relief in individuals with chronic neuropathic pain	5 RCT studies with 184 participants with chronic NPP Attrition Rate: NR	Independent Variables: Inhaled Cannabis Dependent Variables: Pain scores	Pain scores: spontaneous pain intensity scales Used Bayesian probability modeling to meta-analyze	Based on data from 178 patients with 405 total observed responses, the authors estimated the odds ratio for a more than 30% reduction in pain	provides evidence that inhaled cannabis results in short-term reductions in chronic neuropathic pain for 1 in	Bayesian meta-analysis of individual patient data from 5 randomized trials suggests that inhaled	Level of Evidence: I Strengths: Adequate sample size with 405 observed responses, sophisticate

	<ul style="list-style-type: none"> • Searched 4 databases • Selected only RCTs investigating chronic painful neuropathy • Excluded multiple sclerosis related neuropathy • Utilized Bayesian probability modeling for meta-analysis 	<p>Setting: Clinical trials in various settings</p>		<p>the data from 5 RCTs</p>	<p>scores in response to inhaled cannabis versus placebo for chronic painful neuropathy as 3.2 with a Bayesian credible interval.</p> <p>Authors estimated the posterior probability of effect of Cannabis for chronic painful neuropathy to be 99.7% and the Bayes factor as 332.</p>	<p>every 5 to 6 patients treated (number needed to treat = 5.6 with a Bayesian 95% credible interval ranging between 3.4 and 14</p>	<p>cannabis may provide short-term relief for 1 in 5 to 6 patients with neuropathic pain. Pragmatic trials are needed to evaluate the long-term benefits and risks of this treatment.</p>	<p>d data analysis, various neuropathies assessed with differing RCTs</p> <p>Weaknesses: Dosage and mode of administration may influence pain relief, Bayesian meta-analysis may be subjective, assessed only the short-term usage of cannabis on NPP</p> <p>Feasibility: Supports that future research should be done to prove cannabis efficacy; however, treating individuals</p>
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								with multiple types of NPP is warranted with cannabis and implementation is obtainable
Nugent et al, ¹⁹ 2017	<p>SR</p> <p>Purpose: effects of plant-based cannabis on pain relief in individuals with chronic pain</p> <ul style="list-style-type: none"> • Searched 6 databases from inception until 2016 • Included intervention trials and observational studies that reported pain, quality of life, or adverse effect outcomes 	<p>75 studies included (13 SR, 27 RCT, 35 Observational studies), specific patient number not reported</p> <p>Attrition Rate: NR</p> <p>Setting: mainly clinical setting</p>	<p>Independent Variables: plant-based cannabis</p> <p>Dependent Variables: Pain scores, adverse effects</p>	<p>Pain scores: VAS and NRS</p> <p>Adverse effects: Adverse effect checklist</p> <p>Utilized Cochran chi-square test; analysis done with Stata/IC</p>	<p>In the largest RCT, 246 patients with peripheral neuropathic pain self-titrated nabiximols up to a maximum dosage of 24 sprays per day or received a placebo. Those who completed the study (79 in the nabiximols group and 94 in the placebo group) and responded positively to the intervention had a significant decrease in pain (odds ratio, 1.97 [CI, 1.05 to 3.70]). However, among all participants, including those</p>	<p>There is low-strength evidence that cannabis alleviates neuropathic pain but insufficient evidence in other pain populations. According to 11 systematic reviews and 32 primary studies, harms in general population studies include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment.</p>	<p>Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain. Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects</p>	<p>Level of Evidence: I</p> <p>Strengths: Sample size, various patient populations with NPP, multiple pain scales used, strict inclusion criteria</p> <p>Weaknesses: Not enough evidence that blatantly supports the use of cannabis for NPP, limited assessment of harms because of lack of elderly participants</p>

					<p>who did not have an intervention response, the reduction in the NRS pain score did not reach clinical or statistical significance. The second largest RCT with low ROB included 55 patients with HIV-associated sensory neuropathy who were randomly assigned to smoke either 3.56% THC cigarettes or a placebo 3 times per day for 5 days. Among those who completed the study, 52% (n=13) of the treatment group had a clinically significant reduction in pain compared with 24% (n=6) of the placebo group. A 1-year prospective cohort study (n=431) of patients with nociceptive</p>			<p>Feasibility: Implementing CBD into NPP management regimens is obtainable.</p>
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					and neuropathic chronic non-cancer pain provides information about long-term treatment effects. Cannabis users had a reduction in average pain intensity (using a visual analogue scale from 0 to 10) that was stable across 4 time points over 1 year, but the change was small and not clinically significant (0.92 [CI, 0.62 to 1.23]).			
Wallace et al, ¹⁴ 2015	<p>RCT</p> <p>Purpose: effect of inhaled cannabis versus a placebo on pain intensity scores in individuals with painful diabetic peripheral neuropathy</p> <ul style="list-style-type: none"> Administered either high, medium, or low doses of 	<p>16 patients with painful diabetic painful NPP</p> <p>Attrition Rate: 0</p> <p>Setting: Outpatient study at the University of California, San Diego Medical Center</p>	<p>Independent Variables: inhaled cannabis (1%, 4% and 7% THC)</p> <p>Dependent Variables: Pain scores, cognitive testing results</p>	<p>Pain scores: VAS scores</p> <p>Cognitive testing results: Trail-Making test and Paced Auditory Serial Attention Test</p> <p>ANCOVA models to regress change was used for analysis</p>	<p>There was significant difference in spontaneous pain scores between doses [$p < 0.001$]. Specifically, average pain intensity score in the placebo dose was 0.44 points higher than the pain score in the low dose [$p = 0.031$], 0.42 points higher as</p>	<p>Significant decrease in pain scores between doses. There was significant difference between placebo versus low, medium, and high doses. There was a significant negative effect of the high dose on two of</p>	<p>This small, short-term, placebo-controlled trial of inhaled cannabis demonstrated a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-</p>	<p>Level of Evidence: II</p> <p>Strengths: Double-blind placebo evaluating both pain scores and cognitive function, inhalational method of vaporization well tolerated and</p>

	<p>cannabis, or a placebo</p> <ul style="list-style-type: none"> • Measured pain intensity scores at 5, 15, 30, 45, and 60 minutes, then every 30 minutes for 3 more hours 				<p>compared to the medium dose [$p = 0.04$], and 1.2 points higher as compared to the high dose [$p < 0.001$]. There was no statistical difference between the low and the medium dose [$p = 0.92$], but the average pain score in the high dose was 0.73 and 0.75 points lower than the average scores in the low and the medium doses, respectively [both $p < 0.001$]. The overall effect of dose on pain remained significant [$p < 0.001$] after controlling for prior dose level, which was also a significant predictor of pain [$p < 0.001$]. On the dose level, only the differences in pain scores between high dose and other</p>	<p>the three neuropsychological tests.</p>	<p>refractory pain. This adds preliminary evidence to support further research on the efficacy of the cannabinoids in neuropathic pain.</p>	<p>avoids combustion and subsequent carbon monoxide</p> <p>Weaknesses: vaporization inconvenient in clinical settings, only a single dose study so hard to draw definitive conclusions</p> <p>Feasibility: Implementing CBD into NPP management regimens is obtainable.</p>
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					<p>doses remained significant.</p> <p>Using a less conservative pairwise analysis and adjusting for visit order and baseline scaled score [time = 0], performance on the PASAT during placebo differed from medium [d = -1.03, p = .024] and high doses [d = -1.14, p = .008] at 15 minutes, while Trail Making Part B differed between placebo and high dose only at 120 minutes [d = -1.15, p = 0.009]</p>			
Sainsbury et al, ¹⁵ 2021	SR with MA Purpose: effect of THC, cannabidiol, and synthetic cannabinoids on pain intensity scores in individuals with chronic neuropathic pain	17 studies including 861 patients with NPP Attrition Rate: NR Setting: United States, Israel, England, Germany, Denmark,	Independent Variables: THC, cannabidiol, synthetic cannabinoid Dependent Variables: Pain intensity scores	Pain intensity scores: VAS and NRS Cochran's Q test and the 12 statistic were used for analysis	Overall, THC/CBD significantly improved pain intensity by -6.6 units compared to placebo on a 0–100 scale (P < .001). Two studies reported the number of patients with a 30% reduction in	Significant reduction in pain intensity for THC/CBD and dronabinol compared to the placebo. No significant difference between CBD and synthetic CBD versus the placebo.	Although THC and THC/CBD interventions provided a significant improvement in pain intensity and were more likely to provide a 30%	Level of Evidence: I Strengths: Sample size, multiple cannabis-based medication studies, multiple pain score scales used,

	<ul style="list-style-type: none"> • Searched 4 databases from inception to 2021 • Included only placebo-controlled RCTs 	<p>Belgium, Czech Republic; combined clinical and outpatient setting</p>			<p>pain intensity. Patients who used THC/CBD were 1.756 times more likely to achieve a 30% reduction in pain compared to patients receiving placebo (P = .008). Patients receiving THC/CBD intervention were 1.422 times more likely to achieve a 50% reduction in pain, although the difference was not statistically significant [58] (P = .37). There were no significant differences in the change in pain disability index (0-70) from baseline with THC/CBD compared to placebo in two studies [49,58] (P = .06), nor in the change in Brief Pain Inventory (BPI)</p>		<p>reduction in pain, the evidence was of moderate-to-low quality. Further research is needed for CBD, dronabinol, CT-3, and CBDV.</p>	<p>promising initial results</p> <p>Weaknesses: moderate-to-low quality of evidence so hard to draw definitive conclusions, variability in length of studies, small sample sizes of individual studies used in SR, variable routes of administration and dosages/number of doses</p> <p>Feasibility: Implementing CBD into NPP management regimens is obtainable.</p>
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					pain intensity score [61](P = .29) and BPI pain interference score (P = .184).			
Schimrigk et al, ¹⁶ 2017	<p>RCT Purpose: effect of dronabinol versus placebo in pain intensity scores for individuals with multiple sclerosis-induced neuropathy</p> <ul style="list-style-type: none"> Administered dronabinol and a placebo over a 16-week period and then compared the difference in pain intensity based on an 11-point numerical rating scale 	<p>240 individuals with MS-induced NPP entered trial</p> <p>Attrition Rate: Only 85 individuals completed entire trial; reasons included: adverse events, lack of compliance, withdraw informed consent, exclusion criteria met, did not reach dose range, and other</p> <p>Setting: combined clinical and outpatient setting; study completed in Europe (Austria/Germany)</p>	<p>Independent Variables: Dronabinol</p> <p>Dependent Variables: Pain intensity, adverse effects</p>	<p>Pain intensity: 11-point NRS-PI scale</p> <p>Adverse effects: adverse effects checklist</p> <p>Analysis was done with a 2-sample t test and a Wilcoxon-Rank sum test</p>	<p>The primary endpoint “mean change of pain intensity from baseline to mean of weeks 1–16” compared between dronabinol (1.92 ± 2.01; 30%) and placebo (1.81 ± 1.94; 27%) was not statistically significant ($p = 0.6760$). The observed pain reduction was clinically relevant in both groups. During long-term follow-up, pain intensities remained at a low level (range 2.5–3.8). the QoL assessment (SF-36) showed a clear improvement during the double-blind period from baseline until end of treatment</p>	<p>Pain intensity scores were reduced over the 16-week trial period without significant difference between the dronabinol and placebo groups. Adverse reactions were higher in the dronabinol group compared to placebo, but these reactions decreased with long-term use. No signs of drug abuse and only one possible case of dependency</p>	<p>trial demonstrated the long-lasting therapeutic potential, the good tolerability and favorable safety profile of dronabinol – especially in terms of drug abuse and dependency. Based on the presented results, there is no special focus on the harm caused by dronabinol treatment. Although the statistical proof of efficacy for dronabinol versus placebo</p>	<p>Level of Evidence: II</p> <p>Strengths: Clinically relevant decrease in pain intensities, unbiased results with placebo, occurrence of severe and serious adverse effects was rare and decreased with long-term follow-up</p> <p>Weaknesses: High attrition rate, pronounced placebo analgesia, adverse effects unrelated to pharmacological action seen in</p>

				<p>in both groups (physical component summary: verum: -3.50, placebo: -3.18; mental component summary: verum: -2.69, placebo: -0.60) without significant difference.</p> <p>During double-blind and open-label period 92.9% of patients experienced at least one AE. In the double-blind period, the proportion of patients experiencing AEs was higher in the dronabinol group than in the placebo group. The proportion of patients experiencing SAEs was low. ARs were more frequently observed in the verum group compared to the</p>	<p>treatment is pending, physicians should consider the potential benefits of the multifactorial effects of dronabinol</p>	<p>placebo group</p> <p>Feasibility: Implementing CBD into NPP management regimens is obtainable.</p>
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					placebo group. SARs were very rare and occurred only in 3 patients (dysphoria, constipation, exacerbation of preexisting neuropathic pain).			
Aviram et al, ¹⁷ 2017	<p>SR with MA Purpose: analyze the efficacy and adverse events of cannabis-based medicines for chronic and postoperative pain</p> <ul style="list-style-type: none"> Utilized PubMed/Medline and Google Scholar up until 2015 Included double-blind, placebo-controlled RCTs 	<p>Included 43 RCTs with a total of 2,437 patients with chronic pain</p> <p>Attrition Rate: NR</p> <p>Setting: various clinical and outpatient settings</p>	<p>Independent Variables: Cannabis-based medicines</p> <p>Dependent Variables: Pain scores, adverse effects</p>	<p>Pain scores: VAS and NRS</p> <p>Adverse effects: Number of adverse effects experienced in each sample</p> <p>Analysis done using Comprehensive Meta-Analysis Version 3 software</p>	<p>7 studies included in this review reported significant (30–50%) pain reduction in a substantial part of their patients. These studies showed that chronic cancer pain patients with poorly controlled opioid treatment consistently showed that low doses of nabiximols yielded significant analgesic effects. They also showed, by accumulated case reports of RCTs, that administration of oro mucosal</p>	<p>Showed limited evidence showing more pain reduction in chronic pain, especially by inhalation compared to a placebo. While some RCTs showed a clinically significant decrease in pain scores, 30-50%, or more, did not show an effect. The most prominent adverse effects were central nervous and gastrointestinal problems.</p>	<p>The current systematic review suggests that CBMs might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain (NP) patients. Additionally, GI AEs occurred more frequently when CBMs were administered via oral/oro mucosal routes than by inhalation.</p>	<p>Level of Evidence: I</p> <p>Strengths: Adequate sample size with various types of chronic pain, results showed decrease in pain levels supporting further research and possible support for implementation into practice</p> <p>Weaknesses: Failure of included studies to report patient's prior use of</p>

					<p>spray of THC and CBD separately, yielded 50% pain reduction in 16 of 34 chronic NP patients. The studies showed that NP patients treated with ajulemic acid yielded 30% pain reduction in 50% of the sample compared to 20% of the sample by placebo. Ellis showed that HIV NP patients yielded NNT of 3.5 for 30% pain reduction by cannabinoids inhalation over placebo. Zajicek showed that MS patients reported significant clinical pain reduction by orally administered cannabis extract in 28% of the sample, compared to 17.2% in placebo.</p>			<p>CBD, inadequate blinding of placebo because of stigma surrounding cannabis by patients,</p> <p>Feasibility: Implementing CBD into NPP management regimens is obtainable.</p>
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					<p>More than half of the studies (28 of 43 RCTs) included in this review reported on AEs that were experienced by the patients in their studies. The most commonly reported AEs were for the central nervous system (CNS) and the gastrointestinal system (GI). Other AEs were divided into groups by psychological, musculoskeletal, cardiac, vision, and hearing AEs. No separate analyses were performed for each particular AE because of the large variety of AEs; furthermore, some of the AEs were similar, but were referred to with different definitions between studies. Thus, a combined analysis was</p>			
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					performed for each affected group. The results showed a significantly higher harm by CBMs over placebo for all the above-mentioned systems, except for the musculoskeletal and cardiac systems.			
<p>RCT = Randomized Control Trial; SR = Systematic Review; MA = Meta-Analysis; THC = δ-9-tetrahydrocannabinol; fMRI = functional Magnetic Resonance Imaging; NR = Not Reported; MS = Multiple Sclerosis; NPP = Neuropathic Pain; VAS = Visual Analog Scale; NRS-PI = Numeric Rating Scale for Pain Intensity; ANOVA = Analysis of Variance; CBD = Cannabinoid</p>								

Organizational Assessment

Primary DNP Project Goal

While neuropathic pain has many different pathophysiology's for its origin of disease, the first line pharmacological treatments for this disease are often gabapentin and pregabalin.²⁰ The goal of this DNP project is to incorporate cannabinoids as an effective adjunct, or replacement, for the above listed drugs. The evidence compiled by the author shows that pain scores are often decreased with administration of cannabinoids and there are various routes of administration available for this patient population. The current clinical site does not incorporate cannabinoids in the treatment plan for patients with NPP; so, the aim of the project is to educate anesthesia providers consulted for pain management in this patient population to feature cannabinoids to improve the pain scores and overall quality of life.

Goals and Outcomes

There are multiple goals and desired outcomes for this project, as stated above. By educating anesthesia providers involved with pain management of patients on the benefits of cannabinoids, this will ultimately benefit their future patients. Upon completion of this education module, the anesthesia providers will know the benefits of cannabinoids for patients suffering from neuropathic pain and their advantages, and differences, when compared with current popular medication regimens. The anesthesia providers will also be educated on the potential side effects of cannabinoids and their counterparts (gabapentin, pregabalin). These goals and outcomes should be considered both attainable and achievable based on the literature supporting the use of cannabinoids to positively impact NPP patient's pain scores.^{10-12,14,16} These goals and outcomes would be deemed relevant as they are directly related to improving pain scores of individuals with NPP through the administration of cannabinoids. These goals and

outcomes should only take about 20 minutes to achieve, as that is how long the entire education module is.

Program Structure

The program structure is simple as this is an educational module with a pre-test, an educational PowerPoint, and a post-test to assess if the educational PowerPoint presentation was effective. The strength of this structure is that it will make relaying information about cannabinoids in relation to neuropathic pain easy and attainable. A video presentation of a PowerPoint is a quick and effortless way to educate anyone. Some weaknesses of a short PowerPoint educational module is the inability of the participants to ask questions to the author as they are receiving the information. An additional weakness is that anesthesia providers can have pretty busy schedules, so getting participants that may not be interested in the topic may also be difficult. An opportunity of this educational module is that cannabinoids are not regularly used by anesthesia providers for pain management, so this will educate them on a new potential avenue to treat their patients with neuropathic pain. This is also an opportunity to educate anesthesia providers on a drug class that they may be unfamiliar with because of the newer research that has been conducted since cannabinoids have gained eligibility for medical, and recreational, use. Some threats to this educational module are that some of the desired participants may have preconceived notions about cannabinoids and may not want to branch out to broaden their treatment regimens. Cannabinoids have often had a negative stigma related to their use, but new research has proven their medicinal benefits. For the purpose of this educational module, cannabinoids benefits for patients with neuropathic pain is the focus, but desired anesthesia provider participants may already have skepticism regarding cannabinoid use in their patients.

Methodology for Proposal

The setting for this educational module is computer-based, so the participants could complete this at home or at work (at their convenience). In total, this educational module will only take 20 minutes. The participants will be anesthesia providers that could potentially be involved with pain management for individuals with neuropathic pain. Potential patients could be in a pain clinic, preoperative pain management, or postoperative pain management with neuropathic pain.

As stated above, the approach of the project and procedures will be a computer-based, PowerPoint educational module. There will be a pre-test containing 10 questions, the educational PowerPoint, then a 10-question post-test. The pre and post-tests will adequately assess if the anesthesia provider understood the information provided and assess if they are more likely to prescribe cannabinoids based on the new information received.

The participants will be recruited through an anesthesia company and the risks and benefits for the participants will be explained. There will be minimal risk, as expected with any educational intervention. These risks can vary from mild emotional distress to mild physical discomfort due to sitting while participating in the online module. The participants would need to consent to partaking in this learning experience and will be ensured that the results from their pre and post-tests will be kept confidential.

The data collected will only be the answers from the pre and post-tests and compare their results for each participant. One of the questions will assess how likely they are to use the new information in practice, so that is an additional assessment. There will also be demographic questions such as gender, age, and ethnicity to help evaluate and organize the data. The data will

be kept by the author. Analysis is not necessary for this project as the only evaluation tool is the pre and post-tests which are straight forward.

The implications for advanced nursing practice would be to see if this information provided in the educational module will see a difference in practice. If the answers provided in the post-test do not see an increase in provider perception of cannabinoid usage in this patient population, it may have no impact on advanced nursing practice. However, if the education module leads to the anesthesia providers using cannabinoids for patients with NPP, this may lead to other advanced nurse practitioners to utilize this drug. Eventually, cannabinoids may be used for a plethora of pain conditions and may become a mainstay in medication regimens.

Timeline

The timeline of this educational module should take about 1 year and 6 months. From June 2022 to December 2022, research will be gathered by the author to support the education provided in the module. From January 2023 to April 2023, the research will continue to be reviewed and the educational module will be constructed. In addition to this, Institutional Review Board (IRB) approval will be worked towards, including all of the necessary forms. Starting in May 2023, the educational module will begin to be disseminated to the desired participants. From May 2023 to August 2023, the educational module will continue to be disseminated and results gathered from the pre and post-tests from the individuals. From September 2023 to November 2023, the results will be gathered and examined by the author to assess the success of their educational module. In December 2023, the results from the educational module will be shared with the faculty and other doctoral candidates.

Results

Demographics

A total of 4 Certified Registered Nurse Anesthetists (CRNAs) responded to the previously described educational module. A total of 65 surveys were sent to anesthesia providers, with a response rate of 6%. All 4 of the participants consented to the survey and completed it until completion. The average age of the participants was 35, with the range from 30-40 years of age. In total, 3 of the participants were male (75%), and one female (25%). The ethnicity breakdown was 2 Hispanic (50%) and 2 Caucasian (50%). All of the participants have received their doctorate and their length of time practicing in anesthesia ranged from 0-5 years of experience. Three of the participants had 0-2 years of experience (75%), and one participant had 2-5 years of experience (25%). The demographic results are also portrayed in Table 1.

Table 1. Demographic Results

Participants (Total = 4)	Number	Percentage (%)
Gender		
Male	3	75
Female	1	25
Ethnicity		
Caucasian	2	50
Hispanic	2	50
Position		
CRNA	4	100
Level of Education		
Doctorate	4	100
Years of Experience		
0-2	3	75
2-5	1	25

Knowledge of Neuropathic Pain

There were a total of 3 questions constructed to test the knowledge of NPP for the participating anesthesia providers. The results of these questions indicated that the participants had a strong base knowledge of the difficulty in managing the pain of those suffering from NPP and the challenges in diagnosing it. There was a knowledge deficit in the prevalence of NPP in the general United States population; however, the results signified that the participants thought this disease was more prevalent than it is.

The first question testing the participants' knowledge of NPP asked how many individuals suffer from NPP in the United States. Before the educational module, only one individual (25%) was correct in answering the question, which was 30 million. The other answer choices selected were 50 million (2 participants, 50%), and 100 million (1 participant, 25%). After the educational module, the post-test results showed an increase in knowledge about prevalence with 3 participants (75%) choosing 30 million. One individual chose 100 million in the post-test. The other two questions related to knowledge of NPP were based on diagnosis and difficulty with treatment. The second question asked what the gold standard for diagnosing NPP is, with the correct answer being "there is no gold standard for diagnosing." All four participants answered correctly in both the pretest and post-test. The third question asked why the pain management of NPP is so difficult. The correct answer was "all of the above" with the following being the other answer choices: treating underlying pathology is difficult due to many cases being idiopathic in nature, NPP is known to be refractory to both pharmacological and non-pharmacological pain interventions, and there is no definitive treatment regarding medications (gabapentin, pregabalin, etc.). All four participants also answered this question correctly in both the pretest and post-test. The specific breakdown of these results are depicted in Table 2.

Table 2. Knowledge of Neuropathic Pain

Question	Pretest	Post-test
1. An estimated how many individuals in the United States suffer from Neuropathic Pain (NPP)?		
<i>30 million</i>	<i>1 (25%)</i>	<i>3 (75%)</i>
50 million	2 (50%)	0
100 million	1 (25%)	1 (25%)
150 million	0	0
2. What is the gold standard for diagnosing NPP?		
MRI of brain and spine	0	0
Meeting a specific criteria describing pain	0	0
Blood test measuring excess substance P	0	0
<i>There is no gold standard for diagnosing NPP</i>	<i>4 (100%)</i>	<i>4 (100%)</i>
Why is the pain management of NPP so difficult?		
Treating underlying pathology is difficult due to many cases being idiopathic in nature	0	0
NPP is known to be refractory to both pharmacological and non-pharmacological pain interventions	0	0
There is no definitive treatment regarding medications (gabapentin, pregabalin, etc.)	0	0
<i>All of the above</i>	<i>4 (100%)</i>	<i>4 (100%)</i>

Knowledge of Cannabinoids

The participants' knowledge of cannabinoids was tested more extensively than NPP with a total of 6 questions. The questions ranged from side effects, mechanism of action, routes of administration, and obstacles to uses in clinical practice. The baseline knowledge of the participants before the educational module was fair. There are two questions based on the mechanism of action and two questions on side effects. The participants struggled with one question in each category but were knowledgeable about the second question. Overall, there was

a vast improvement in question correctness between the pretest and post-test, indicating successful education module implementation.

The first question in this category asked what the main reason cannabinoids have not made their way into common clinical practice. Three participants (75%) chose the correct answer in both the pretest and post-test; the answer was "limited research due to legality of medication." One participant (25%) chose "large pharmaceutical companies do not want to use it" in both the pretest and post-test. The question related to the route of administration asked if a patient had a diagnosis of Chronic Obstructive Pulmonary Disease (COPD), which route of administration would you prescribe to your patient? In the pretest, 2 participants (50%) chose incorrectly, with the answer choice being oral. The correct answer was "oral and sublingual" with 2 participants (50%) choosing correctly in the pretest, and all four (100%) choosing this answer in the post-test.

As stated previously, there were 2 questions related to side effect knowledge of cannabinoids. The first question compared the side effects of cannabinoids and gabapentin and asked which side effect they had in common. Two participants (50%) chose weight gain in the pretest, which was incorrect. The correct answer was impaired memory, with two participants (50%) choosing correctly in the pretest, and all 4 (100%) choosing correctly in the post-test. The second question was true or false and stated that cannabinoids have no side effects. The correct answer was false, and all four participants (100%) chose correctly in both the pretest and post-test.

Lastly, there were 2 questions to test the knowledge of the mechanism of action of cannabinoids. The first question asked how cannabinoids elicit their desired effect. The correct answer was the influx of calcium. Unfortunately, no participant chose this during the pretest. But with a successful educational module, all four participants (100%) answered correctly in the

post-test. In the pretest, two of the participants (50%) chose sodium influx and two participants (50%) chose chloride influx as their incorrect answers. The second question related to the mechanism of action was true or false and stated that cannabinoids work on the presynaptic CB1 and CB2 receptors. The correct answer was true, and all 4 participants (100%) chose the correct answer in both the pretest and post-test. All of the above data about participant knowledge of cannabinoids is also illustrated in Table 3

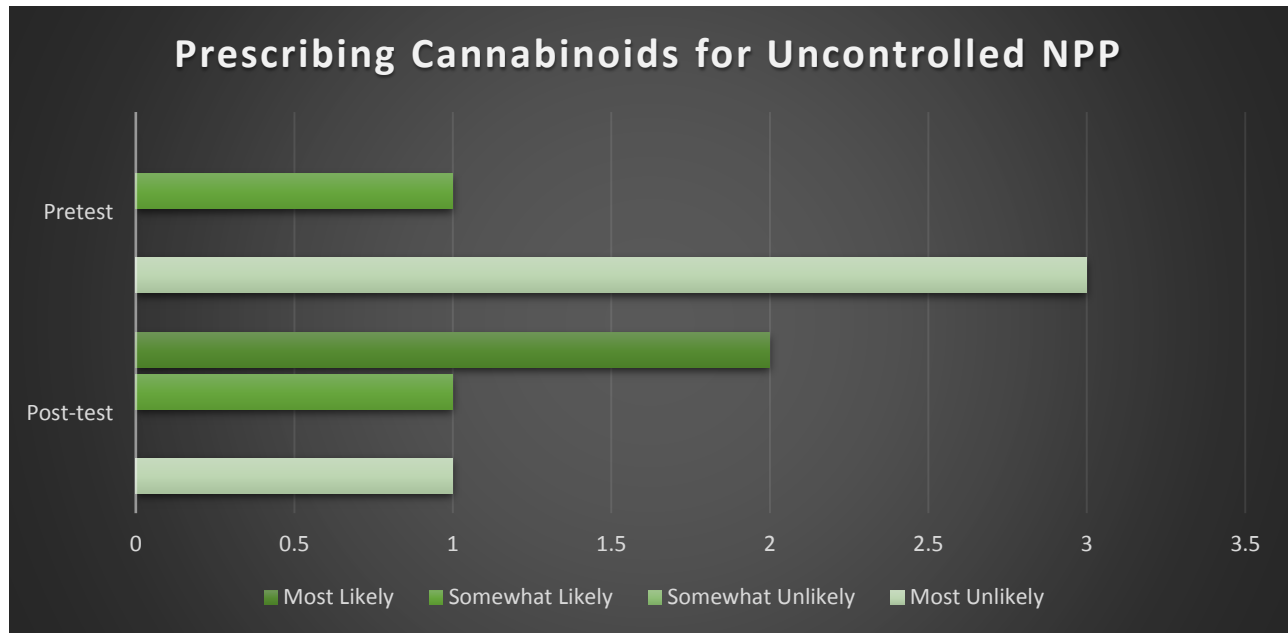
Table 3. Knowledge of Cannabinoids

Question	Pretest	Post-test
What is one of the main reasons cannabinoids (CBs) have not made their		
Patients do not want to use it	0	0
Large pharmaceutical companies do not want to use it	1 (25%)	1 (25%)
<i>Limited research due to legality of medication</i>	3 (75%)	3 (75%)
Not shown to be effective	0	0
A side effect that CBs and gabapentin have in common is:		
Weight gain	2 (50%)	0
<i>Impaired memory</i>	2 (50%)	4 (100%)
Blurred vision	0	0
Coughing	0	0
None of the above		
Cannabinoids elicit their desired effects by reducing the influx of which of the following:		
Potassium	0	0
Sodium	2 (50%)	0
Chloride	2 (50%)	0
<i>Calcium</i>	0	4 (100%)
Cannabinoids have no side effects		
True	0	0
<i>False</i>	4 (100%)	4 (100%)
Cannabinoids work on the presynaptic CB1 and CB2 receptors.		
<i>True</i>	4 (100%)	4 (100%)
False	0	0

Which route of administration would you prescribe to an individual with COPD?		
Oral	2 (50%)	0
Inhalational	0	0
Sublingual	0	0
<i>Oral and sublingual</i>	2 (50%)	4 (100%)

Perception Towards Cannabinoids

The overall objective of the educational module is to adequately treat neuropathic pain. For this to be done, those involved in pain management (anesthesia providers) must prescribe the interventions to accomplish this. Cannabinoids cannot be used as a successful adjunct to pain management therapies if it's not prescribed by those involved in the care of these patients. To assess this, the participants were asked how likely they would be to prescribe a cannabinoid to a patient with NPP whose current pain control is inadequate. In the pretest, one participant (25%) answered they are somewhat likely to prescribe a cannabinoid, and three of the participants (75%) answered they were most unlikely to prescribe a cannabinoid. After viewing the educational module, the participants were again asked the same question in the post-test. In the post-test, two participants (50%) said they were most likely to prescribe a cannabinoid, one participant (25%) answered they were somewhat likely, and one (25%) still answered they were most unlikely to prescribe a cannabinoid. These results are also shown in Table 4.

Table 4. Perception Towards Cannabinoids

Overall Statistics

The participant's knowledge of both neuropathic pain and cannabinoids was shown to be improved through the use of the educational module by analyzing the pretest versus the post-test. There was a total of 9 knowledge-based questions. With 4 participants, that would equate to a possible 36 correct answers in both the pretest and the post-test. The specific answer choices were relayed above; however, the cumulative statistics will give a more sufficient overall depiction of the knowledge gained. In the pretest, there was a total of 24 correct answers out of 36 equaling a 66.67% correct response rate. After viewing the educational module, this increased to 34 correct answers out of 36 equaling a correct response rate of 94.44%. This shows an overall increase of 27.77% indicating the successful education of the participants. This increase in knowledge of both neuropathic pain and cannabinoids also lead to a shift in the anesthesia providers' perception of cannabinoids. In the pretest, only 1 out of 4 (25%) of the participants answered that they would be either somewhat likely or most likely, to prescribe

cannabinoids to this patient population. After viewing the education module, this increased to 3 out of 4 (75%) of the participants answering they were either somewhat likely or most likely, to prescribe cannabinoids.

Discussion

Cannabinoids continue to gain momentum in the healthcare industry due to increases in research supporting their usefulness. This research must be disseminated to providers and patients so that informed decisions can be made to optimize patient care while sustaining patient safety. This educational module showed that anesthesia providers can utilize cannabinoids to help their patients, but they must be educated on both its benefits and its risks. Although the education process to becoming an anesthesia provider is quite extensive, cannabinoids are not necessarily a focal point in their education regimen due to the lack of definitive research stating their usefulness. Additionally, in the experience of this particular author, the education provided while learning anesthesia care and pain management focuses on intravenous and oral administration for immediate pain relief in a post-operative setting and peripheral nerve blocking for chronic pain. However, there are anesthesia providers involved in chronic pain management for patients due to their expertise in treating acute pain. For these anesthesia providers to obtain knowledge in a variety of pain management techniques, additional resources outside of the educational setting (school) are necessary to provide new material. The educational module analyzed above showed that anesthesia providers may be open to prescribing their patients cannabinoids to treat their pain in the correct situation, but they must be educated on the benefits and usefulness of the drug. Cannabinoids are not a staple for pain management and most anesthesia providers would not elect to use a drug they are not familiar with. Anesthesia

providers must continue to push forward and alter therapies when new evidence shows potential benefits to their patients.

Limitations

While the results of the above educational module were promising due to the perceived increase in knowledge and willingness to use cannabinoids, the sample size was extremely small. The educational module cannot be a definitive success due to the lack of ability to generalize the results to a larger pool of participants. The desired participants are often bombarded with countless research projects and surveys in a short period, and it's impossible to complete all of them. Additionally, the majority of the emails used to disseminate the educational module were the work email of the desired participants, which are utilized much less frequently than personal emails. As for limitations of the actual educational module, having a pretest and post-test with the same questions and answers taken about 10 minutes apart may not be the best indicator of knowledge acquisition. To see if the participants obtained and retained the desired information, more time should pass before retaking the test. However, this could lead to incomplete surveys if the participants do not complete the post-test at a later date. Lastly, while the online setting is extremely beneficial for the convenience of information dissemination, it limits the participants' ability to ask questions or provide feedback to improve the educational module.

Implications for Practice

The initial next step to be taken for this Quality Improvement (QI) project would be to educate a larger amount of anesthesia providers. As stated in the limitation's sections above, the number of providers that completed the survey in its entirety was limited. Although the results show that the participants progressed in their knowledge of cannabinoids and neuropathy, a larger sample would need to be had to make any definitive statements about the success of this

QI educational module. Once a larger audience has been educated, the next steps would be to evaluate changes in practice with the individuals that are involved with pain management of patients with neuropathic pain. In terms of sustaining changes in practice, the plan would be to have this educational module available as a yearly pain management module that could be put towards continuing education requirements for license renewals.

This educational module could have implications in a variety of advanced practice nursing specialties. Anesthesia providers are not the only providers involved in the pain management of patients with neuropathic pain. This educational module could be targeted to any provider involved in prescribing medications to help patients with neuropathic pain optimize their medication regimens.

Conclusion

While neuropathic pain continues to impact a significant number of patients and lacks definitive pain control, cannabinoid research continues to grow and gain support in pain management of a plethora of disease states. The research that joins cannabinoids and the successful treatment of neuropathic pain continues to grow but is still in the early stages and lacks the sustained pain management success of other drugs such as gabapentin and pregabalin. Nonetheless, there is also research supporting the use of cannabinoids as an adjunct to these medications for patients with neuropathic pain. Anesthesia providers can be of use in the realm of pain management. To successfully manage pain, providers must be aware of a variety of interventions to best serve their patients. Educational modules relaying information, in this case about cannabinoids and their safety/effectiveness, seem to be a sufficient, cost-effective approach to grow the expertise of those involved in pain management while potentially improving patient care and maintaining patient safety

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Appendix

IRB FIU Approval

**MEMORANDUM**

To: Dr. Fernando Alfonso

CC: Austin Miller

From: Carrie Bassols, BA, IRB Coordinator *ceb*

Date: March 2, 2023

Proposal Title: "Cannabinoids for Pain Management in Patients with Neuropathic Pain: An Evidence-Based Educational Module"

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #: IRB-23-0077 **IRB Exemption Date:** 03/02/23
TOPAZ Reference #: 112830

As a requirement of IRB Exemption you are required to:

- 1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
- 2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
- 1) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at <http://research.fiu.edu/irb>.

IRB Anesthesia Group Approval

February 7, 2023

Fernando Alfonso, DNP, CRNA, APRN
Clinical Assistant Professor
Department of Nurse Anesthesiology
Florida International University

Dr. Fernando Alfonso,

Thank you for inviting Envision Anesthesia to participate in the Doctor of Nursing Practice (DNP) project conducted by Austin Miller entitled "Cannabinoids for pain management in patients with neuropathic pain" in the Nicole Wertheim College of Nursing and Health Sciences, Department of Nurse Anesthesiology at Florida International University. I have granted the student permission to conduct the project using our providers.

Evidence-based practice's primary aim is to yield the best outcomes for patients by selecting interventions supported by the evidence. This proposed quality improvement project seeks to utilize the latest literature to increase providers awareness regarding cannabinoid use for pain control in patients with neuropathic pain.

We understand that participation in the study is voluntary and carries no overt risk. All Anesthesiology providers are free to participate or withdraw from the study at any time. The educational intervention will be conveyed by a 15-minute virtual PowerPoint presentation, with a pretest and posttest questionnaire delivered by a URL link electronically via Qualtrics, an online survey product. Responses to pretest and posttest surveys are not linked to any participant. The collected information is reported as an aggregate, and there is no monetary compensation for participation. All collected material will be kept confidential, stored in a password encrypted digital cloud, and only be accessible to the investigators of this study: Austin Miller, RN, BSN and Dr. Fernando Alfonso, DNP, CRNA, APRN

Once the Institutional Review Board's approval is achieved, this scholarly project's execution will occur over two weeks. Austin Miller will behave professionally, follow standards of care, and not impede hospital performance. We support the participation of our Anesthesiology providers in this project and look forward to working with you.

A handwritten signature in blue ink that reads 'Suzanne Hale'.

Suzanne Hale, MSN, CRNA, ARNP
Advanced Practice Provider Director, Broward and Dade
Chief, Memorial Regional Hospital
Envision Physician Services
954-265-2044

Informed Consent



CONSENT TO PARTICIPATE IN A QUALITY IMPROVEMENT PROJECT CANNABINOIDS FOR PAIN MANAGEMENT IN PATIENTS WITH NEUROPATHIC PAIN: AN EVIDENCE-BASED EDUCATIONAL MODULE

SUMMARY INFORMATION

Things you should know about this study:

- **Purpose:** Educational module to increase providers awareness of the use of cannabinoids to manage neuropathic pain.
- **Procedures:** If the participant chooses to participate, they will be asked to complete a pretest, watch a voice PowerPoint, and then a post test
- **Duration:** This will take about a total of 20 minutes total.
- **Risks:** There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may include mild emotional stress or mild physical discomfort from sitting on a chair for an extended period.
- **Benefits:** The main benefit to you from this research is increase the participants knowledge on cannabinoids and their potential benefits in managing neuropathic pain.
- **Alternatives:** There are no known alternatives available to the participant other than not taking part in this quality improvement project.
- **Participation:** Taking part in this quality improvement project is voluntary.

Please carefully read the entire document before agreeing to participate.

NUMBER OF STUDY PARTICIPANTS:

If the participant decides to be in this study, they will be one of 10 people in this research study.

PURPOSE OF THE PROJECT

The participant is being asked to be in a quality improvement project. The goal of this project is to increase providers' knowledge on the use of cannabinoids and their incorporation into pain management regimens in patients suffering from neuropathic pain. If you decide to participate, you will be 1 of approximately 10 participants.

DURATION OF THE PROJECT

The participation will require about 20 minutes

PROCEDURES

If the participant agrees to be in the project, PI will ask you to do the following things:

1. Complete an online 10 question pre-test survey via Qualtrics, an Online survey product for which the URL link is provided
2. Review the educational PowerPoint Module lasting 10 minutes via Qualtrics, an Online survey product for which the URL link is provided.

3. Complete the online 10 question post-test survey via Qualtrics, an Online survey product for which the URL link is provided.

RISKS AND/OR DISCOMFORTS

The main risk or discomfort from this research is minimal. There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may include mild emotional stress or mild physical discomfort from sitting on a chair for an extended period.

BENEFITS

The following benefits may be associated with participation in this project: an increased participants knowledge on the benefits of utilizing cannabinoids to address pain management issues in individuals with neuropathic pain, and as a result, increasing patient satisfaction with their pain management. The overall objective of the program is to increase the providers' knowledge based on the current literature.

ALTERNATIVES

There are no known alternatives available to the participant other than not taking part in this project. However, if the participant would like to receive the educational material, it will be provided to them at no cost.

CONFIDENTIALITY

The records of this project will be kept private and will be protected to the fullest extent provided by law. If, in any sort of report, PI might publish, it will not include any information that will make it possible to identify the participant. Records will be stored securely, and only the project team will have access to the records.

PARTICIPATION: Taking part in this quality improvement project is voluntary.

COMPENSATION & COSTS

There is no cost or payment to the participant for receiving the health education and/or for participating in this project.

RIGHT TO DECLINE OR WITHDRAW

The participation in this project is voluntary. The participant is free to participate in the project or withdraw the consent at any time during the project. The participant's withdrawal or lack of participation will not affect any benefits to which you are otherwise entitled. The investigator reserves the right to remove the participant without their consent at such time that they feel it is in their best interest.

RESEARCHER CONTACT INFORMATION

1. If you have any questions about the purpose, procedures, or any other issues relating to this research project, you may contact Austin Miller at (386)-216-8204 or amill251@fiu.edu and Dr. Fernando Alfonso, DNP, CRNA, APRN Clinical Assistant Professor at (305)-348-3510 or falfonso@fiu.edu.

IRB CONTACT INFORMATION

If the participant would like to talk with someone about their rights pertaining to being a subject in this project or about ethical issues with this project, the participant may contact the FIU Office of Research Integrity by phone at 305-348-2494 or by email at ori@fiu.edu.

PARTICIPANT AGREEMENT

I have read the information in this consent form and agree to participate in this study. I have had a chance to ask any questions I have about this study, and they have been answered for me. By clicking on the “consent to participate” button below I am providing my informed consent.

Recruitment Letter



Nicole Wertheim College of Nursing & Health Sciences

CANNABINOIDS FOR PAIN MANAGEMENT IN PATIENTS WITH NEUROPATHIC PAIN: AN EVIDENCE-BASED EDUCATIONAL MODULE

Dear Envision Anesthesia Perioperative Providers:

My name is Austin Miller, and I am a student from the Anesthesiology Nursing Program Department of Nurse Anesthesiology at Florida International University. I am writing to invite you to participate in my quality improvement project. The goal of this project is to increase health care providers' awareness on the use of cannabinoids to help manage pain levels in individuals with neuropathic pain. You are eligible to take part in this project because you are a part of the Envision Anesthesia perioperative providers.

If you decide to participate in this project, you will be asked to complete and sign a consent form for participation. Next, you will complete a pre-test questionnaire, which is expected to take approximately 5 minutes. You will then be asked to view an approximately 15 minutes long educational presentation online. After going through the educational module, you will be asked to complete the post-test questionnaire, which is expected to take approximately 5 minutes. No compensation will be provided.

Remember, this is completely voluntary. You can choose to be in the study or not. If you'd like to participate or have any questions about the study, please email or contact me at (386) 216-8204 or amill251@fiu.edu

Thank you very much.

Sincerely,

Austin Miller

(386) 216-8204 or amill251@fiu.edu

Survey Questions



Pretest and Posttest Questionnaire:

Cannabinoids for Pain Management in Patients with Neuropathic Pain: An Evidence-Based Educational Module

INTRODUCTION

The primary aim of this QI project is to increase providers awareness utilizing cannabinoids to improve the pain management of those suffering from neuropathic pain.

Please answer the question below to the best of your ability. The questions are either in multiple choice or true/false format and are meant to measure knowledge neuropathic pain and cannabinoid advantages.

PERSONAL INFORMATION

1. **Gender:** Male Female Other _____
2. **Ages 25 and above:** _____
3. **Ethnicity:** Hispanic Caucasian African American Asian
Other _____
4. **Position/Title:** CRNA Anesthesiologist Resident
Anesthesiologist Assistant
5. **Level of Education:** Certificate Bachelors Masters DNP PhD
6. How many years have you been a perioperative provider?
Over 10 5-10 years 2-5 years 1-2 years

QUESTIONNAIRE

1. An estimated how many individuals in the United States suffer from Neuropathic Pain

(NPP)?

- a. 30 million
 - b. 50 million
 - c. 100 million
 - d. 150 million
- 2. What is one of the main reasons cannabinoids (CBs) have not made their way into common clinical practice?**

- a. Patients do not want to use it
- b. Large pharmaceutical companies do not want to use it
- c. Limited research due to legality of medication
- d. Not shown to be effective

3. A side effect that CBs and gabapentin have in common is:

- a. Weight gain
- b. Impaired memory
- c. Blurred vision
- d. Coughing
- e. None of the above

4. Cannabinoids elicit their desired effects by reducing the influx of which of the following:

- a. Potassium
- b. Sodium

- c. Chloride
 - d. Calcium
- 5. Cannabinoids have no side effects. True or False**
- 6. Cannabinoids work on the presynaptic CB1 and CB2 receptors. True or False**
- 7. How likely are you to prescribe a cannabinoid to an individual with neuropathic pain whose pain control is inadequate?**
- a. Most likely
 - b. Somewhat likely
 - c. Somewhat unlikely
 - d. Most unlikely
- 8. Which route of administration would you prescribe to an individual with COPD?**
- a. Oral
 - b. Inhalational
 - c. Sublingual
 - d. A and C
- 9. What is the gold standard for diagnosing NPP?**
- a. MRI of brain and spine
 - b. Meeting a specific criteria describing pain
 - c. Blood test measuring excess substance P
 - d. There is no gold standard for diagnosing NPP
- 10. Why is the pain management of NPP so difficult?**
- a. Treating underlying pathology is difficult due to many cases being idiopathic in nature

- b. NPP is known to be refractory to both pharmacological and non-pharmacological pain interventions
- c. There is no definitive treatment regarding medications (gabapentin, pregabalin, etc.)
- d. All of the above

DNP Educational Module PowerPoint

Cannabinoids for Pain Management in Patients with Neuropathic Pain: An Evidence-Based Educational Module

Austin Miller, MSN, RN
Fernando Alfonso, DNP, CRNA, APRN



Learning Goals

- From this quality improvement project, you will:
 - Discuss cannabinoids (CB)
 - Understand the benefits of utilizing cannabinoids to treat individuals with neuropathic pain
 - Understand potential side effects of cannabinoids
 - Describe when it may be appropriate to prescribe cannabinoids to an individual suffering from neuropathic pain (NPP)



Background

Pain is a hypersensitivity to abnormal stimuli and nociceptive/Neuropathic response to non-noxious stimuli

Over 50% of NPP patients taking gabapentin are unhappy with pain control

Cannabinoids still considered "experimental" but newer data proving its efficacy controlling pain in this patient population

Cannabinoid side effect profile may be more tolerable to individuals than traditional treatment methods (gabapentin)



Scope of the Problem

- No gold standard diagnostic test, but estimated 10% population has NPP
- 25-46% NPP cases idiopathic in nature
- Refractory to medical management with many patients having inadequate pain control
- With lack of definitive treatment, potentially millions of patients suffering with day-to-day activities



Cannabinoids

- Multiple routes of administration:
 - Inhaled, sublingual, and oral pills
- Binds to presynaptic terminal CB receptors, CB1 and CB2
 - Reduces calcium influx and increases potassium efflux
 - Leads to decreased cellular excitability
 - Also effects endogenous CB postsynaptic to be produced and transported retrograde to also bind with presynaptic CB receptors
- These effects lead to analgesia and antinociceptive effects






The diagram illustrates the mechanism of action of cannabinoids. It shows a presynaptic neuron and a postsynaptic neuron. Synthetic cannabinoids (1) bind to CB1 receptors on the presynaptic terminal, leading to the inhibition of neurotransmitter release (2). Endogenous cannabinoids (3) are released from the postsynaptic neuron and bind to CB2 receptors on the presynaptic terminal, leading to the inhibition of neurotransmitter release (4). Endogenous cannabinoids (5) also bind to CB1 receptors on the postsynaptic neuron, leading to the inhibition of neurotransmitter release (6). The diagram also shows that endogenous and exogenous cannabinoids reduce neuronal signaling (7).



Cannabinoid Efficacy

Multiple randomized-control trials and systematic reviews show evidence of decreased pain scores in NPP patients taking CB

Inhalational shown to have more immediate effect when compared with sublingual and oral route

In addition to decreased pain scores, patients reported increased quality of sleep and a positive impact on day-to-day activities

Utilizing a functional MRI, graph theory analyses found a reduction in network connectivity in areas involved in pain processing



Cannabinoid Dosing

- These alternative routes and subsequent doses have shown to be effective in the literature:
 - Oral
 - Nabilone 0.5-1 mg/week
 - Dronabinol 5-15 mg/day
 - Inhaled
 - 1%, 4%, 7% THC content (varies)
 - Sublingual
 - Cannabidiol 30 mg
 - THC 1 mg



Cannabinoids vs. Gabapentin

Shown to work well as adjuncts to one another when just gabapentin is not controlling patients' pain level

Many patients shown to stop taking gabapentin due to inability to tolerate side effects

CB can either be used as an alternative to traditional NPP medications (gabapentin, pregabalin) or in conjunction



Cannabinoid vs. Gabapentin Side Effects

CB Side Effects	Gabapentin Side Effects
<ul style="list-style-type: none"> Difficulty concentrating Impaired memory Hallucinations/delusions Nausea/vomiting Breathing problems if using inhaled CBs 	<ul style="list-style-type: none"> Somnolence Nausea/vomiting and diarrhea Blurred vision and dry mouth Weight gain Impaired memory



Take Home Points

- Cannabinoids can be an efficacious alternative or adjunct to traditional medication regimens in those suffering with NPP
- CBs have been shown to successfully decrease pain levels, increase sleep quality, and alter brain network activity to positively impact pain scores
- CBs are not the ultimate solution to treating NPP as there are still patients that were not satisfied with their pain control after CB administration
- Side effects of CBs may or may not be more tolerable than gabapentin as this will be individually based
- Treatment plans involving CBs must be individualized to patients in terms of route of administration, dosing, side effect toleration, and desired pain goals



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DNP Dissemination Module PowerPoint

Cannabinoids for Pain Management in Patients with Neuropathic Pain: An Evidence-Based Educational Module


Austin Miller, MSN, RN
Fernando Alfonso, DNP, CRNA, APRN



1

Problem

- Neuropathic pain (NPP) is a hypersensitivity to abnormal stimuli and nociceptive response to non-noxious stimuli
- Over 50% of NPP patients taking gabapentin are unhappy with pain control
- No gold standard diagnostic test, but estimated 10% population has NPP
- 25-46% NPP cases idiopathic in nature



2


Problem and Potential Solution

Refractory to medical management with many patients having inadequate pain control

With lack of definitive treatment, potentially millions of patients suffering with day-to-day activities

Cannabinoids (CB) still considered "experimental" but newer data proving its efficacy controlling pain in this patient population


Cannabinoid side effect profile may be more tolerable to individuals than traditional treatment methods (gabapentin)



3

Cannabinoid Background


- Multiple routes of administration:
 - Inhaled, sublingual, and oral pills
- Binds to presynaptic terminal CB receptors, CB1 and CB2
 - Reduces calcium influx and increases potassium efflux
 - Leads to decreased cellular excitability
 - Also effects endogenous CB postsynaptic to be produced and transported retrograde to also bind with presynaptic CB receptors
- These effects lead to analgesia and antinociceptive effects



4

Cannabinoid Research

- Multiple randomized-control trials and systematic reviews show evidence of decreased pain scores in NPP patients taking CB
- Inhalational shown to have more immediate effect when compared with sublingual and oral route
- In addition to decreased pain scores, patients reported increased quality of sleep and a positive impact on day-to-day activities
- Utilizing a functional MRI, graph theory analyses found a reduction in network connectivity in areas involved in pain processing



5

Project Purpose


- Cannabinoids are not a prominent component of pain management therapy, but new research is showing it can be an effective alternative, or adjunct, to commonly used medications
 - Anesthesia providers are involved in pain management both in hospital settings and pain clinics
- An effective education module highlighting information on both neuropathic pain and cannabinoid efficacy may offer anesthesia providers an adequate alternative to treat their patients that is not currently part of their pain management repertoire



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PICO


Population (P)	Anesthesia providers involved in pain management
Intervention (I)	Prescribing cannabinoids to patients with NPP who have uncontrolled pain
Comparison (C)	None
Outcomes (O)	Improved pain scores and outcomes for these patients with NPP



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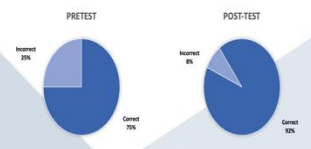

Methods

- A literature review was conducted to review the efficacy of cannabinoid administration in individuals with inadequate pain control secondary to neuropathic pain
- With this information, an online educational module was constructed and disseminated to practicing anesthesia providers
- There was a pretest and a post-test to assess the degree of learning that took place and any shifts in attitude
- This educational module was developed through an anesthesia company and utilized an anonymous, online platform for delivery and data collection.





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Neuropathic Pain Knowledge Results

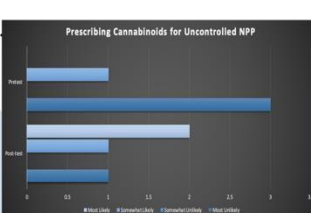

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Cannabinoids Knowledge Results

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Perception of Cannabinoid Results

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Discussion

- Cannabinoids continue to gain momentum in the healthcare industry due to increases in research supporting their usefulness
- This research must be disseminated to providers and patients so that informed decisions can be made to optimize patient care while sustaining patient safety
- Although the education process to becoming an anesthesia provider is quite extensive, cannabinoids are not necessarily a focal point in their education regimen due to the lack of definitive research stating their usefulness
 - Education focuses on intravenous and oral medications for immediate pain relief in the perioperative period and peripheral nerve blocks for chronic pain management



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Discussion

- Anesthesia providers are involved in chronic pain management for patients due to their expertise in treating acute pain
- For these anesthesia providers to obtain knowledge in a variety of pain management techniques, additional resources outside of the educational setting (school) are necessary to provide new material
- The educational module highlighted above showed that anesthesia providers may be open to prescribing their patients cannabinoids to treat their pain in the correct situation, but they must be educated on the benefits and usefulness of the drug
- Cannabinoids are not a staple for pain management and most anesthesia providers would not elect to use a drug they are not familiar with
- Anesthesia providers must continue to push forward and alter therapies when new evidence shows potential benefits to their patients

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Limitations

- Sample size of this educational module was extremely small
 - Cannot generalize about the definitive success to a larger pool of participants
- Participants may be overwhelmed with countless research projects and surveys in a short period of time, affecting the sample size
- Dissemination technique of using work emails may be limiting as personal emails are most likely more frequently used
- Pretest and post-test being 10 minutes apart with the same questions and answers may not be an effective technique for measuring knowledge acquisition
 - While more time between may measure retained information, this may also lead to incomplete surveys
- Online setting limits the participants' ability to ask questions and provide feedback about the educational module

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Conclusion

- Cannabinoid research continues to grow and gain support in pain management for many different disease states
 - Neuropathic pain and cannabinoid research continues to grow but the research is still in the early stages and lacks the sustained success of other drugs (gabapentin, pregabalin)
 - There continues to be research showing the success of cannabinoids as an adjunct with these medications for those suffering from NPP

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Conclusion

- With anesthesia providers playing a role in the realm of pain management, they must be aware of the variety of interventions at their disposal
- Educational modules seem to be a sufficient, cost-effective approach to growing their expertise
 - This in turn improves patient care while maintaining patient safety

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Questions?

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Thank You!

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