EFFICACY AND TOLERABILITY OF SELECTED CANNABINOIDS FOR PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

A Dissertation

Presented to

The Faculty of the Graduate School

University of the Immaculate Conception

Davao City

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in Pharmacy

FERLIEN MAE B. BRIETA

May 2022

UNIVERSITY OF THE IMMACULATE CONCEPTION
Bonifacio St., Davao City
GRADUATE SCHOOL

APPROVAL SHEET

This dissertation titled, **"EFFICACY AND TOLERABILITY OF SELECTED CANNABINOIDS FOR PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS,"** of the University of the Immaculate Conception prepared and submitted by **FERLIEN MAE B. BRIETA** in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmacy, has been examined and is recommended for approval and acceptance.

MOHD MAKMOR BAKRY, PhD
Adviser

APPROVED by the dissertation committee on oral examination with a grade of **PASSED**.

AVEE JOY B. DAYAGANON,PhD
Chairperson

RENAN P. LIMJUCO, PhD
Member

EMMA V. SAGARINO, DBM
Member

MONA L. LAYA, PhD
Member

SHAMIN M. SAFIAN, PhD
Member

ACCEPTED and **APPROVED** in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmacy.

Comprehensive Examination: **PASSED**

AVEE JOY B. DAYAGANON,PhD
Dean, Graduate School

May 2022

ACKNOWLEDGEMENT

The researcher would like to thank the people who played significant roles in her post-graduate studies. The journey of an educational endeavor is challenging and must be overcome. All these people's holistic skills and abilities have made this dissertation writing more insightful. A comprehensive and humbling experience indeed. The researcher is grateful for the education, motivation, and direction extended by the following:

The researcher's dissertation adviser, Professor Mohd Makmor Bakry. Despite his hectic schedule, his commitment to extending his expertise is exceptionally valuable;

The researcher would like to express her sincerest gratitude to Dr. Avee Joy Dayaganon, Dr. Mona Laya, Dr. Emma Sagarino, Dr. Renan Limjuco, and Professor Shamin Saffian, technical experts of the review committee. They have provided the researcher with comprehensive, impressive, and professional recommendations to achieve the best outcomes;

The researcher would like to express her sincerest gratitude to Dr. Felix Chavez for serving as the study's Statistician. For the generosity of his time and sharing his immense knowledge without hesitation;

The researcher would like to express her most profound gratitude to her husband, Glenn Jay Brieta, for his enduring support and inspiration. Thanks to her parents, siblings, children, and classmates, which radiate positivity and hope. They are all instruments of God and allow the victory of this journey;

The researcher expresses heartfelt gratitude to Dr. Avee Joy Dayaganon, Dean of Graduate School, for sharing us wisdom and constantly helping the pioneering batch of PhD in Pharmacy to achieve our academic goals;

Above all, to the Almighty GOD for HIS bountiful blessings that made this research possible.

FMBB

DEDICATION

This study is wholeheartedly devoted to my precious parents, Alfredo and Minda, who have constantly been my source of inspiration and strength. Their continuous moral, spiritual, emotional, and financial support has helped us finish this research.

I lovingly dedicate this research to my husband, Glenn, for the tremendous effort and patience shown to me unconditionally. To my children, Niño and Xavier, who inspire me to better myself every day.

I ultimately dedicate this research to the Almighty God for his guidance, power of the mind, and protection.

All of these, I offer to you.

FMBB

ABSTRACT

Pain management is a complicated challenge for clinicians and a severe limitation to patients' lives; thus, cannabinoids were developed because they efficiently reduce chronic pain. However, the subject stays highly contentious in the public and clinical settings due to constraints in evidence and education. Hence, a systematic review and meta-analyses of double-blinded placebo-controlled randomized controlled clinical trials were undertaken to assess the efficacy of cannabinoids in pain management and patients' tolerability to the therapy. Databases such as ScienceDirect, PubMed, and the US CLINICAL TRIALS were searched from January 2015 to March 2022. After implementing PRISMA, studies with adult participants experiencing any type of pain with pain intensity measured using a numerical rating scale were included. Seven trials were reviewed, and qualified studies underwent meta-analyses for efficacy and tolerability. The pooled overall effect measure for efficacy of pain management revealed an SMD= -0.44 ($p < 0.05$) in favor of Cannabinoids compared to placebo. The pooled overall effect measure for patient tolerability on therapy revealed a Risk ratio= of 1.007 ($p > 0.05$), with no significant difference in the tolerability between cannabinoids and placebo. The two meta-analyses manifested substantial heterogeneity and publication biases that serve as a limitation of this review.

Keywords: Pharmacy Education, cannabinoids, pain management, sativex, nabiximols, cannabidivarin, dronabinol, systematic review, meta-analysis, efficacy, tolerability, Philippines

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Background of the Study

Current pain treatments cannot meet the objectives of pain management among patients suffering from chronic pain. Disappointingly, the quantity and quality of evidence supporting the use of opioids for cancer pain are low, according to a recent overview of systematic Cochrane reviews. In clinical practice, most patients will achieve adequate pain relief with opioids, but a small but significant percentage do not have sufficient pain relief. Antidepressants, anticonvulsants, and opioid analgesics are medications of choice (Finnerup, 2015). However, they often lack efficacy and are limited by side effects, such as respiratory depression, addiction, and sedative effects, resulting in extensive additional costs and reduced quality of life (Carter et al., 2014). There is a strong demand for new analgesics and pain-relieving approaches that can efficiently enhance opioids in patients with insufficient pain relief of cancer pain (Wiffen et al., 2017).

Approximately 40 percent of the population suffers from pain linked to different conditions. This data from the Center for Disease Control and Prevention could target pain management interventions. Malignant pain could happen if cancer grows and destroys the tissue and the organ. The tumor also releases chemicals that cause pain (González-Cano et al., 2021). Neuropathic pain is a painful condition that's usually chronic. It is generally caused by chronic, progressive nerve disease and can also occur as the result of injury or infection. Its incidence is likely to increase due to the aging global population, increased

diabetes mellitus, and improved survival from cancer after chemotherapy (Colloca, 2017). Several studies published in the Clinical Journal of Pain state that the label of non-neuropathic pain includes several pathological conditions, ranging from fibromyalgia to low-back pain and irritable bowel syndrome, where the pain is a prominent, highly disabling symptom.

Integrating Cannabinoids to manage pain can be a valuable opportunity to improve patient outcomes. The use of cannabinoids in treating various conditions dated back thousands of years in Eastern traditional medicine and was introduced to Europe in the 1800s (Guys et al., 2004). Over the past several decades, there has been a renewed interest in the medical use of cannabis for various conditions, including pain ((Kalant, 2001). The earliest clinical studies that evaluated the antinociceptive properties of cannabinoids were limited by inadequate sample size and an insufficient assortment of cannabinoids available for use (Fa et al., 2001). Among different cannabinoids identified in the cannabis plant, Tetrahydrocannabinol (THC) is the most famous and principal psychoactive compound found naturally in the cannabis plant. Cannabidiol, cannabinol, and their synthetic derivatives are the most active in humans. It can exert a moderating effect on pain by activating pathways on cannabinoid receptors scattered all over the body (Kaminska et al., 2015) and then play critical pain management (Wang et al., 2019).

On the other hand, two reviews from Hazekamp (2010) and Amar (2006) reported contradictory conclusions from the conclusions presented by the studies mentioned earlier. There is no significant pain reduction, hence the low efficacy of

CBM for treating various pain conditions, including postoperative, visceral, cancer, and neuropathic pain (NP). The most recent systematic review included clinical trials of cannabinoids for chronic neuropathic pain and chronic (non-cancer) pain related to fibromyalgia, rheumatoid arthritis, and diverse sources. Moreover, additional systematic reviews have been published, including novel delivery methods and patient conditions. In the study of Mucke (2018), the findings were uncertain whether herbal cannabis reduces mean pain intensity. Also, Herbal cannabis and placebo did not differ. In another study, results showing a low risk of bias showed that adding cannabinoids to opioids did not reduce cancer pain (Boland et al., 2020). To date, the amount and quality of evidence on cannabinoids for chronic pain have been low, with the evidence compromised by studies of short duration and small patient numbers, as well as a negative result for pain relief as reported by a meta-analysis of two more extensive trials (Mücke et al., 2016). Insufficient data to assess pain reduction activity, safety, and tolerability among all ages is apparent at this point (Köstenberger et al., 2021).

The chronological changes in the results mentioned above show an interesting trend in the beneficial effect of cannabinoids on pain, notwithstanding the years of research and the research gaps. First, no conclusive published data on head-to-head comparison between the different cannabis integrated medicines, such as cannabinoids from different cultivars, or different forms and preparations of cannabinoids. The next gap is on insufficient outcome measures and inclusion criteria used in different studies, limiting the overall comparison to determine the best utilization of cannabinoids as medicine. Another gap is identified on incidence

and dropouts from therapy as a function of tolerability as a secondary outcome to pain reduction is not established. The last gap is in the interventions used; newly discovered cannabinoids (Cannabidivarin in 2020) and newly approved by FDA are not included in the aforementioned analyses (Cannabidiol in 2018).

Accordingly, there is a definite need to establish data to concretize the evidence-based practice of Cannabinoids. Patients, Pharmacists, and Clinicians need to be aware of the pieces of evidence available to utilize the substance rationally. Given these considerable uncertainties, the researcher has seen the need to address the research gaps identified and assess the efficacy and tolerability of selected Cannabinoids in managing pain among patients of any age. Hence, a systematic review and meta-analysis research is conducted. This research is disseminated to Patients, pharmacists, clinicians, and Government and Non-Government Organizations to help raise awareness. Furthermore, the researcher looks forward to promoting the importance of acknowledging Paracelsus' "The Dose Makes the Poison" concept.

Review Question

The study explore studies on efficacy and tolerability of Cannabinoids and proposes this question below for the investigation to be established:

In patients suffering from pain, what is the efficacy and tolerability of different cannabinoid derivatives compared to placebo control?

Review of Related Studies

This section presents scientific background of the different elements of the scope of the research. These information provides fundamental basis and structure to various components of the research scope.

Types of Pain

In the study by Argoff (2017), Statistics estimated that 100 million adults are suffering from chronic pain in the United States in the pain management community. However, with all of the recent negative attention on pain management, insufficient energy and attention have been focused on perhaps one of the more daunting aspects of chronic pain, the actual assessment, and treatment of the person in pain. Therefore, it is reasonable to acknowledge that managing chronic pain in today's healthcare system is challenging as we increasingly understand the complexity of pain. It has become increasingly clear that chronic pain does not refer to one disorder or underlying mechanism and cannot be assessed or treated with a one-size-fits-all approach. Advances in our understanding have led to new, more effective patient assessment and treatment strategies.

However, considerably more work needs to be done to implement truly individualized approaches to patient care concerning pain management. Among the most challenging aspects of treating a person in pain is identifying the type(s) and mechanism(s). Notably, distinguishing between neuropathic and non-neuropathic pain types and understanding if a person has features of both can better allow for more tailored treatment. When considering the responses to

determine a course of treatment, be mindful that multimodal therapy may be required for optimal care. Since there are various potential origins for the pain with similar symptom profiles and distinct mechanisms that drive pain, devising a personalized treatment may be hard to come by. However, we must still have multidimensional assessments covering these components, which is imperative to our ultimate goal.

Ideally, despite the complexity of established and current knowledge, selecting an appropriate medication to address chronic pain regimens does not mean allowing this approach in all instances. Remedies may include commonly used analgesics, such as aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs); opioids may be more effective for more severe pain. So-called adjuvant analgesics (e.g., anticonvulsants or antidepressants) may also be considered. However, there may be individual differences in response to these drugs, depending on the patient's neuropathic and non-neuropathic pain profile. Nociceptive pain, a non-neuropathic pain, is generally more responsive to anti-inflammatory agents and classical opioids, while neuropathic pain may be less responsive to traditional pain management. In some cases, pharmacologic agents that address more than 1 type of pain may be more effective for some patients, and many newer medicines are designed to target both types of pain in a single pill.

Chronic Pain. Over 100 million people in the United States would meet the criteria for chronic pain syndrome. History and physical exam should include the onset of pain, description, mechanism of injury if applicable, location, radiation

of pain, quality, severity, factors contributing to relief or worsening of the pain, frequency of the pain, and any breakthrough pain. A verbal numeric rating scale (VNRS) or number scale for pain is a standard measure to determine the severity of pain, numbered from zero to ten. This tool is commonly used for pain intensity.

Furthermore, associated symptoms should be assessed, such as muscle spasms or aches, temperature changes, restrictions to range of motion, morning stiffness, weakness, muscle strength, sensation changes, and hair, skin, or nail changes. In addition to the patient's symptoms, the significance of the impact of the pain on day-to-day function should be discussed, as well as a review of the activities of daily living. Our current chronic pain treatments can result in an estimated 30 percent decrease in a patient's pain scores. A thirty percent reduction in pain can significantly improve patients' function and quality of life. Understanding how chronic pain affects the patient's quality of life is essential. There are multiple categories and types of chronic pain, including malignant, neuropathic, nociceptive, musculoskeletal, inflammatory, psychogenic, and mechanical (Dydyk & Conermann, 2021).

Malignant Pain. Pain is a common manifestation of neoplastic disease. Cancer treatments, including cytotoxic chemotherapy, radiation, surgery, and various interventions, may contribute in differing degrees to the development of pain syndromes that are often worsened by daily stressors, anxiety, and depression (World Health Organization, 1996). The prevalence of cancer pain increases depending on the length of patient survival from diagnosis through treatment.

For example, newly diagnosed cancer patients tend to have a lower pain prevalence than patients undergoing active cancer treatment, and patients with the advanced disease report 75 percent, the highest prevalence of pain (Hoffberg, 2015). Like, Opioid analgesics are an efficacious treatment option for cancer pain. For persistent pain, which requires an around-the-clock (ATC) medication regimen, it is preferable to use long-acting formulations to improve patient compliance with potentially less euphoric side effects and reduce concerns of behavior aberrancies. However, these formulations tend to be more expensive and have a greater risk of causing sleep-disordered breathing (central sleep apnea). The dosing frequency may be increased, if necessary, for titration of analgesic control. Additional analgesics are prescribed to treat breakthrough cancer pain (BTP) (Pergolizzi et al., 2013).

Neuropathic Pain. Neuropathic pain is caused by a lesion or disease of the somatosensory system. Its incidence is likely to increase due to the aging global population, increased diabetes mellitus, and improved survival from cancer after chemotherapy. The burden of chronic neuropathic pain seems related to the complexity of neuropathic symptoms, poor outcomes, and complex treatment decisions. Significantly, quality of life is impaired in patients with neuropathic pain due to increased drug prescriptions and visits to health care providers and the morbidity from the pain and the inciting disease. Despite challenges, progress in understanding the pathophysiology of neuropathic pain is spurring the development of new diagnostic procedures and personalized interventions, which

emphasize the need for a multidisciplinary approach to managing neuropathic pain (Colloca et al., 2017).

Consequently, neuropathic pain is associated with increased drug prescriptions and visits to health care providers. Patients typically experience distinct symptoms, such as burning and electrical-like sensations and pain resulting from non-painful stimulations; the symptoms persist and tend to become chronic and respond less to pain medications. Sleep disturbances, anxiety, and depression are frequent and severe in patients with neuropathic pain, and quality of life is more impaired in patients with chronic neuropathic pain than in those with chronic non-neuropathic pain that does not come from damaged or irritated nerves (Attal et al., 2011).

Nociceptive Pain. Neuropathic pain is different from nociceptive pain. Nociceptive pain is a medical term that describes physical or potential damage to the body of non-neuropathic origin. Nociceptive pain is the body's reaction to painful stimuli such as a pulled back muscle or bone, and it does not cause nerve damage. Nociceptive pain is the most common type of pain people experience. It develops when the nociceptive nerve fibers are triggered by inflammation, chemicals, or physical events, such as stubbing a toe on a piece of furniture. Examples might be the pain felt from a sports injury, a dental procedure, or arthritis. Nociceptive pain is usually acute and develops in response to a specific situation. It tends to go away as the affected body part heals. For example, nociceptive pain from a broken ankle gets better as the ankle heals.

The body contains specialized nerve cells called nociceptors that detect noxious stimuli or things that could damage the body, such as extreme heat or cold, pressure, pinching, and chemicals. These warning signals are then passed along the nervous system to the brain, resulting in nociceptive pain. This happens very quickly in real-time, which is why people know to remove their hands if they touch a hot oven or take the weight off an injured ankle (Spahr et al., 2017).

Core Outcome Measures For Chronic Pain Clinical Trials: IMMPACT Recommendations

The core outcome measures should be considered in the design of all clinical trials of the efficacy and effectiveness of treatments for any chronic pain. These core outcome measures are most applicable to clinical trials to determine the efficacy or effectiveness of treatments for chronic pain (Dworkina et al., 2005). Various aspects of pain can change as a result of treatment, and the consequences of reviews of the literature on pain assessment in adults support the recommendation that measures of pain intensity, the use of rescue treatments, pain quality, and the temporal components of pain should be considered when assessing pain outcomes. Self-report measures provide the ‘gold standard for evaluating pain outcomes because they reflect the inherently subjective nature of pain, but they should be supplemented by careful assessments of the use of rescue treatments.

Pain Intensity and Pain Scale. Each of the commonly used methods of rating pain intensity: visual analog scales (VAS), numerical rating scales (NRS), and verbal rating scales (VRS), are reliable and valid, and no one scale

consistently demonstrates more excellent responsiveness in detecting improvements associated with pain treatment (Jensen & Karoly, 2001). However, there are essential differences concerning lost data. More incredible difficulty completing VAS measures is associated with increased age and opioid intake (Jensen & Karoly, 2001). Cognitive impairment is related to the inability to complete NRS ratings of pain intensity (Jensen & Karoly, 2001).

Based on a review of the literature on pain measures prepared for the IMMPACT-II consensus meeting (Jensen, 2003) and discussions among the participants, an 11-point (i.e., 0–10) NRS measure of pain intensity is recommended as a core outcome measure in clinical trials of chronic pain treatments. The specific format of this rating should include a presentation of the numbers from zero to ten, with zero meaning ‘No pain’ and ten meaning ‘Pain as bad as you can imagine,’ accompanied by the instructions (Cleeland & Ryan, 1994). It is recommended that the percentages of patients obtaining reductions in pain intensity from baseline of at least 30 percent be declared when an NRS (or VAS) has been used in a chronic pain clinical trial. To permit comparisons with previous studies and meta-analyses, investigators may also wish to report the percentages of patients obtaining reductions in pain intensity from a baseline of at least 50 percent.

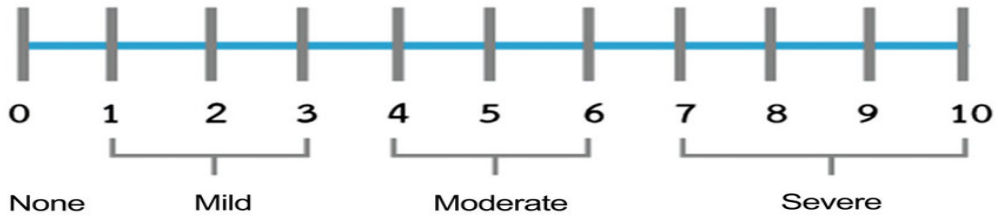


Figure 1. Pain Numerical Rating Scale

Usage of Rescue Analgesics. Rescue medication consumption has been used as an outcome measure in clinical trials, including the amount used and time to use. Scales have been developed that allow quantification of medication use in chronic pain patients based on dosage and medication class, and composite measures have been proposed that combine rescue medication usage and pain intensity ratings into a single score. Although these may be used to compare different treatment groups in clinical trials, the psychometric properties of such composite measures are not well established. Despite the complex issues involved in interpreting rescue medication usage in a clinical trial, patients in a placebo group can be expected to take more rescue treatment than patients administered an efficacious investigational treatment. When considered together with pain intensity rating patients, the amount of rescue treatment can provide an important supplemental measure of the efficacy of the evaluated medicine. For these reasons, assessments of rescue treatments are recommended as a core outcome in trials where rescue interventions are available and permitted.

Physical Functioning. Measures of physical functioning typically assess multiple aspects of function, including activities of daily living. Disturbed sleep is

prevalent in chronic pain patients, and its assessment is also essential in regular pain trials. Individuals with chronic pain consider increased ability to function and improved sleep important treatment objectives. Generic measures provide information about physical functioning and treatment benefits that can be compared across different conditions and studies. Disease-specific measures assess problems associated with specific requirements that may not be evaluated by generic standards and may be more responsive to treatment effects. Because each of these approaches has strengths, the use of disease-specific measures, when available, and generic measures of physical functioning should be considered in designing chronic pain clinical trials. These are the scales valid for physical functioning, the Multidimensional Pain Inventory Interference Scale and Brief Pain Inventory interference items.

Emotional Functioning. Chronic pain is often accompanied by symptoms of psychological distress and psychiatric disorders, including depression, anxiety, and anger. Based on a review of the literature of measures of emotional functioning prepared for the IMMPACT-II, for these reasons, administration of both the Beck Depression Inventory and the Profile of Mood States is recommended in chronic pain clinical trials to assess the significant aspects of the emotional functioning outcome domain. The assessment of emotional functioning in patients with chronic pain presents a challenge because of various symptoms of depression. Such as decreased libido, appetite or weight changes, fatigue, and memory and concentration deficits—are also commonly believed to be consequences of chronic pain and the medications used for its treatment (Gallagher & Verma, 2004).

Participant Ratings of Global Improvement and Satisfaction with Treatment. Global ratings of improvement and satisfaction in a clinical trial provide an opportunity for participants to aggregate all of the components of their experience—pain relief, improvement in physical and emotional functioning, side effects, convenience—into one overall measure of their perception of the advantages and disadvantages of the treatment they received. Based on a review of the literature on global outcome measures prepared for the IMMPACT-II consensus meeting and discussions among the participants, the Patient Global Impression of Change scale is recommended for use in chronic pain clinical trials as a core outcome measure of global improvement with treatment. This measure is a single-item rating by participants of their progress with treatment during a clinical trial on a seven-point scale that ranges from ‘very much improved’ to ‘very much worse’ with ‘no change’ as the midpoint.

Symptoms and Adverse Events

Passive Capture of Spontaneously Reported Adverse Events and Symptoms and Use of Open-Ended Prompts. The assessment, analysis, and reporting of adverse events are essential to all clinical trials. Clinical trial protocols should define the evaluation method and the rationale for that approach. In selecting the technique used for ascertaining adverse events and the methods used for recording and coding the terms used to describe these events, consideration should be given to the type and purpose of the trial, whether international regulatory requirements dictate specific approaches, the phase of development or post-marketing, and the total safety experience with the product.

In describing the results of clinical trials, the incidence of individual and severe adverse events should be reported for each treatment group. It is also essential to evaluate and report the severity of adverse events as this may differ among treatments with a comparable incidence of adverse events. Active capture using structured interviews or questionnaires to assess specific symptoms and adverse events relevant to the disorder or treatment being studied is often more sensitive and informative than passive capture or general inquiries. It is essential to recognize that the frequency, duration, intensity, distress, importance to the patient, impact on daily function, and investigator and patient causal attributions can be assessed for symptoms and adverse events. Such assessments provide information about the clinical importance of safety and tolerability outcomes. The authors recommend that methods for actively capturing signs and adverse events relevant to chronic pain and its treatment be vigorously explored.

Participant Disposition Specified in the CONSORT Guidelines. Chronic pain clinical trials should collect and report comprehensive information on participant disposition. Data on participant disposition is essential for the adequate evaluation of the results of a clinical trial and for interpreting the trial's conclusions regarding efficacy and safety. Although the Consolidated Standards of Reporting Trials (CONSORT) guidelines were developed to serve as a guide to reporting results of clinical trials, they also provide a valuable enumeration of the core elements of information on participant disposition. It should be recorded when conducting trials, including the numbers of participants who withdraw and are lost to follow-up and the reasons for withdrawal and loss.

Detailed information describing the extent to which each participant adhered to the protocol will allow data analyses to be conducted that specifically examine efficacy in patients who adhered to the protocol. Such efficacy-valuable or per-protocol analyses can sometimes be valuable in interpreting the results of intention-to-treat studies, although the benefits of comparing randomized groups are lost. Although reasons for withdrawal are usually provided in reports of clinical trials, this information is often inadequate.

Cannabinoid Derivatives in Medicine

Cannabis or marijuana has been employed for medicinal purposes way back in history, dating back to ancient times. It once held a prominent position in medicine, recommended by many eminent physicians for numerous diseases, particularly headaches and migraine. This plant has taken a fascinating journey through the decades from a legal and frequently prescribed status to illegal, driven by political and social factors rather than science. However, with an abundance of growing support for its medicinal uses, the misguided stigma of cannabis is fading, and there has been a dramatic push for legalizing medicinal cannabis and research. Almost half of the United States has now legalized medicinal cannabis.

Several states have legalized recreational use. Others have legalized cannabidiol-only use, one of many therapeutic cannabinoids extracted from cannabis. Physicians need to be educated on the history, pharmacology, clinical indications, and proper clinical use of cannabis, as patients inevitably inquire about it for many diseases, including chronic pain and headache disorders, for which there is some intriguing supportive evidence. The literature suggests that the

medicinal use of cannabis may have a therapeutic role for many diseases, particularly chronic pain disorders, including headaches. Supporting literature means medicinal cannabis and cannabinoids in several types of headache disorders, including migraine and cluster headache. However, it is primarily limited to case-based, anecdotal, or laboratory-based scientific research. Cannabis contains many pharmacological and biochemical compounds, of which only a minority understand, so many potential therapeutic uses likely remain undiscovered.

Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms of action, and opiate pathways, suggesting potential synergistic or similar benefits. Modulating the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for many new classes of medications. Despite the limited evidence and research suggesting a role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are lacking and necessary for confirmation and further evaluation (Baron, 2015).

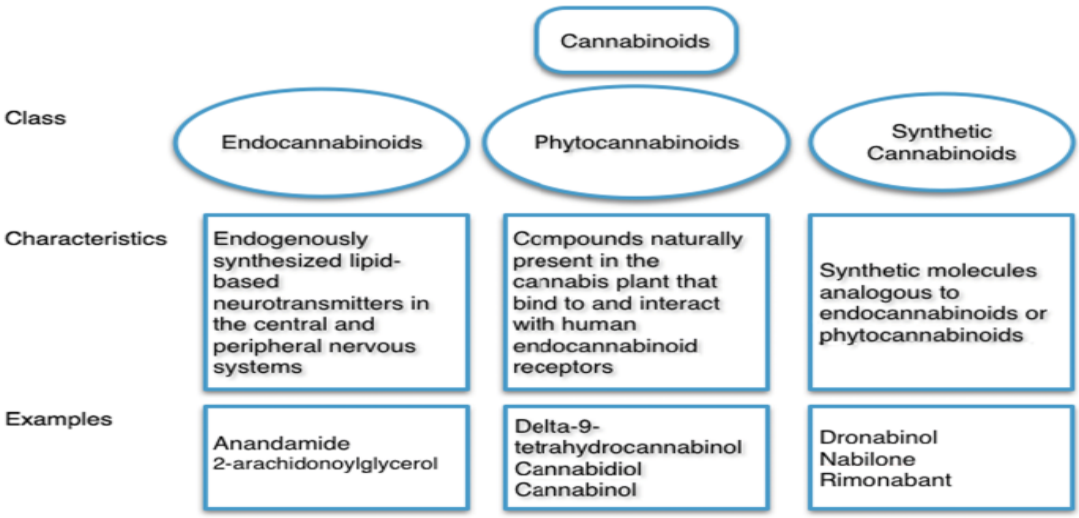


Figure 2. Classification of Cannabinoids

There is a renewed interest in treatments with medical cannabis and cannabinoids. Based on an increasing number of publications over the last decades that permitted new insights into mechanisms, efficacy, and safety of cannabinoids, cannabinergic medications are authorized in an increasing number of European and non-European countries. For thousands of years, alleviating chronic, painful conditions has been one of the primary reasons for the use of cannabis. Depending on the country, a wide range of medicinal cannabis preparations are available: ranging from defined cultivars of medical cannabis, mainly varying in their THC: CBD ratio, that is inhaled or taken as whole-plant extracts, to highly purified single cannabinoids, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), or mixtures of two enriched extracts, standardized to a 1:1 ratio of THC: CBD (Nabiximols).

Although conflicting opinions continue to exist, most reviews concluded that medical cannabis and cannabinoids play a significant role in managing pain. Surprisingly, systematic studies to date do not support an "entourage effect" of the other plant constituents of cannabis (mainly terpenoids) in treating chronic pain. An emerging cannabinoid is CBD, the only cannabinergic medication available that does not cause the typical "cannabis high"; it is not a "controlled substance." However, despite years of research, there is either no study or no well-conducted, head-to-head comparison between different cannabis cultivars, pure cannabinoids, and pure cannabinoids and extracts. It remains unanswered which is the optimal treatment approach (Köstenberger et al., 2021).

In 2017, a National Academies of Sciences, Engineering, and Medicine (NASEM) report comprehensively evaluated the body of evidence regarding cannabis health effects through 2016. Following the literature search from 5 databases and consultation with experts, 11 conditions were identified for evidence compilation and evaluation: amyotrophic lateral sclerosis, autism, cancer, chronic noncancer pain, Crohn's disease, epilepsy, glaucoma, human immunodeficiency virus/AIDS, multiple sclerosis (MS), Parkinson's disease, and posttraumatic stress disorder. The body of evidence for medical cannabis requires more rigorous evaluation before consideration as a treatment option for many conditions. The evidence necessary to inform policy and treatment guidelines is currently insufficient for many states (Okpeku et al., 2021).

Cannabinoid Integrated Medicines for Malignant Pain

Despite medical care improvements, advanced cancer patients still experience substantial symptom distress. There is increasing interest in using medicinal cannabinoids, but there is little high-quality evidence to guide clinicians. Elderly patients suffering from chronic pain conditions such as those associated with cancer may seek medical cannabis treatment. Findings published in the European Journal of Internal Medicine indicated that medical cannabis usage among patients 65 years and older significantly improved their chronic pain and overall quality of life (Abuhasira et al., 2018). The study authors concluded that the therapeutic use of cannabis might be safe and efficacious for relieving chronic pain in the elderly population. As evidenced by the percentage of those who reduced

or stopped using their opioid analgesics, cannabis use may also lead to a decrease in prescription medicines, specifically opioids.

In the same study above, cannabinoids, specifically Cannabidiol, are proposed as an opioid alternative with comparable efficacy and better safety. An initial sample of 131 patients was recruited from a private pain management center's investigative population. Ninety-seven patients completed the 8-week study. The primary inclusion criteria included patients between 30 and 65 years old with chronic pain who have been on opioids for at least one year. Data were collected at three different time points: baseline, 4, and 8 weeks. Opioids and other medication use were evaluated via the medication and psychiatric treatment receipt. Improvement was evaluated using four indices: Pain Disability Index (PDI-4); Pittsburgh Sleep Quality Index (PSQI), Pain Intensity and Interference (PEG); and Patient Health Questionnaire (PHQ-4). Over half of chronic pain patients (53 percent) reduced or eliminated their opioids within eight weeks after adding CBD-rich hemp extract to their regimens.

Almost all CBD users (94 percent) reported quality of life improvements. The results indicated a significant relationship between CBD and PSQI ($p = 0.003$), and PEG ($p = 0.006$). There was a trend toward improvement but no significant relationship between CBD use and PHQ and PDI. CBD could significantly reduce opioid use and improve chronic pain and sleep quality among patients currently using opioids for pain management (Capano et al., 2020).

This study compared the efficacy of a tetrahydrocannabinol: cannabidiol (THC: CBD) extract, a nonopioid analgesic endocannabinoid system modulator,

and a THC extract, with placebo, in relieving pain in patients with advanced cancer (Johnson et al., 2021). In total, 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing, entered a two-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. Patients were randomized to THC:CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59). The primary analysis of change from baseline in mean pain Numerical Rating Scale (NRS) score was statistically significantly in favor of THC: CBD compared with placebo (improvement of -1.37 vs. -0.69), whereas the THC group showed a nonsignificant change (-1.01 vs. -0.69). Twice as many patients taking THC: CBD showed a reduction of more than 30 percent from baseline pain NRS score when compared with placebo (23 [43 percent] vs. 12 [21 percent]).

The associated odds ratio was statistically significant, whereas the number of THC group responders was similar to placebo (12 [23 percent] vs. 12 [21 percent]) and did not reach statistical significance. There was no change from baseline in a median dose of opioid background medication or several doses of breakthrough medication across treatment groups. No significant group differences were found in the NRS sleep quality, nausea scores, or pain control assessment. However, the European Organization for Research and Treatment of Cancer Quality of Life Cancer Questionnaire showed a worsening in nausea and vomiting with THC: CBD compared with placebo (P = 0.02), whereas THC had no difference (P = 1.0) (Greimel et al., 2006). Most drug-related adverse events were mild/moderate in severity. This study shows that THC: CBD extract is efficacious

for pain relief in patients with advanced cancer pain not fully relieved by strong opioids (Johnson et al., 2010).

Cannabinoid Integrated Medicines for Neuropathic Pain

Peripheral neuropathy can significantly impact the quality of life for those affected, as therapies from the current treatment algorithm often fail to deliver adequate symptom relief (Girach et al., 2019). However, there has been an increasing body of evidence for the use of cannabinoids in treating chronic, noncancer pain. This four-week, randomized, and placebo-controlled trial examined the efficacy of a topically delivered cannabidiol (CBD) oil in the management of neuropathic pain. The study population included 62.1 percent males and 37.9 percent females with a mean age of 68. There were a statistically significant reduction in intense pain, sharp pain, cold and itchy sensations in the CBD group compared to the placebo group. No adverse events were reported in this study. The findings demonstrate that the transdermal application of CBD oil can significantly improve pain and other disturbing sensations in patients with peripheral neuropathy. The treatment product was well tolerated and may provide a more practical alternative than other current therapies in treating peripheral neuropathy (Xu et al., 2020).

A clinical trial with dronabinol involving two hundred forty MS patients with central NP entered a 16-week placebo-controlled phase-III study followed by a 32-week open-label period. One hundred patients continued therapy for overall up to 119 weeks. The primary endpoint was the change of pain intensity on the 11-point Numerical Rating Scale over a 16-weeks treatment period. Safety was assessed

based on adverse reactions (ARs), signs of dependency, and abuse. Pain intensity during 16 weeks of dronabinol and placebo treatment was reduced by 1.92 and 1.81 points without a significant difference ($p = 0.676$). Although the proportion of patients with ARs was higher under dronabinol than placebo (50.0 vs. 25.9 percent), it decreased during long-term use of dronabinol (26 percent). No signs of drug abuse and only one possible case of dependency occurred. The trial results demonstrate that dronabinol is a safe long-term treatment option (Schimrigk et al., 2017).

In another experimental randomized placebo-controlled four-way crossover trial, the analgesic effects of inhaled pharmaceutical-grade cannabis in 20 chronic pain patients with fibromyalgia (van de Donk, et al., 2019). Four different cannabis varieties and a placebo variety without any THC or CBD. After a single vapor inhalation, THC and CBD plasma concentrations, pressure and electrical pain thresholds, spontaneous pain scores, and drug high were measured for 3 hours. None of the treatments had an effect greater than placebo on automatic or electrical pain responses.

However, in the same study above, more subjects receiving Bediol displayed a 30 percent decrease in pain scores compared to placebo (90 percent vs. 55 percent of patients, $P = 0.01$), with spontaneous pain scores correlating with the magnitude of drug high ($\rho = -0.5$, $P < 0.001$). Cannabis varieties containing THC caused a significant increase in pressure pain threshold relative to placebo ($P < 0.01$). Cannabidiol inhalation increased THC plasma concentrations but diminished THC-induced analgesic effects, indicative of synergistic

pharmacokinetic but antagonistic pharmacodynamic interactions of THC and CBD. This experimental trial shows the complex behavior of inhaled cannabinoids in chronic pain patients with just small analgesic responses after a single inhalation. Further studies are needed to determine long-term treatment effects on spontaneous pain scores, THC-CBD interactions, and the role of psychotropic symptoms on pain relief (van de Donk et al., 2019).

In the study on Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis (Meng et al., 2017), Eleven randomized controlled trials including 1219 patients were included. There was variability in the studies in quality of reporting, etiology of NP, type, and dose of selective cannabinoids. Patients who received particular cannabinoids reported a significant, but clinically small, reduction in mean numerical rating scale pain scores (0-10 scale) compared with comparator groups (-0.65 points; 95 percent confidence interval, -1.06 to -0.23 points; P = .002, I = 60 percent; Grade of Recommendations Assessment, Development, and Evaluation: weak recommendation and moderate-quality evidence). The use of selective cannabinoids was also associated with improved quality of life and sleep with no major adverse effects. Particular cannabinoids provide a small analgesic benefit in patients with chronic NP. There was a high degree of heterogeneity among publications included in this SR-MA. Well-designed, large, randomized studies are required to evaluate better specific dosage, duration of intervention, and the effect of this intervention on physical and psychological function.

Cannabinoid Integrated Medicines for Non-Neuropathic Pain

To assess the analgesic efficacy and safety of single-dose oral cannabidiol (CBD) as an adjunct to standard care for patients presenting to an emergency department with acute low back pain, the CANBACK trial was done in Austin Hospital, Melbourne (Bebee et al., 2021). A randomized, double-blinded, placebo-controlled clinical trial was done on patients presenting with acute, non-traumatic low back pain between 21 May 2018 and 13 June 2019. One hundred eligible patients were randomized to receive 400 mg CBD or placebo in addition to standard emergency department analgesic medication. Pain score two hours after administration of study agent, on a verbal numerical pain scale (range, 0-10). Secondary outcomes were the length of stay, the need for rescue analgesia, and adverse events. The median age of the 100 participants was 47 years (IQR, 34-60 years); 44 were women. Mean pain scores at two hours were similar for the CBD (6.2 points; 95 percent CI, 5.5-6.9 points) and placebo groups (5.8 points; 95 percent CI, 5.1-6.6 points; absolute difference, -0.3 points; 95 percent CI, -1.3 to 0.6 points). The median length of stay was 9.0 hours (IQR, 7.4-12 hours) for the CBD group and 8.5 hours (IQR, 6.5-21 hours) for the placebo group. Oxycodone use during the four hours preceding and the four hours after receiving CBD or placebo was similar for the two groups, as were reported side effects. CBD was not superior to placebo as an adjunct medication for relieving acute non-traumatic low back pain in the emergency department.

Precise cannabis treatment dosing remains a major challenge, leading to physicians' reluctance to prescribe medical cannabis. To test the

pharmacokinetics, analgesic effect, cognitive performance, and safety effects of an innovative medical device that enables the delivery of inhaled therapeutic doses of Δ9 -Tetrahydrocannabinol (THC) in patients with chronic pain. In a randomized, three-arms, double-blinded, placebo-controlled, cross-over trial, 27 patients received a single inhalation of Δ9 -THC: 0.5mg, 1mg, or a placebo. Δ9 -THC plasma levels were measured at baseline and up to 150-min post-inhalation. Pain intensity and safety parameters were recorded on a 10-cm visual analog scale (VAS) at predefined time points. The cognitive performance was evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB). Evidence suggests that cannabis-based medicines are an effective treatment for chronic pain in adults.

The pharmacokinetics of THC varies as a function of its route of administration. Pulmonary assimilation of inhaled THC causes rapid onset of analgesia. However, currently used ways of cannabinoids delivery provide unknown doses, making it impossible to implement a pharmaceutical standard treatment plan. A novel selective-dose cannabis inhaler delivers significantly low and precise amounts of THC, thus administering inhaled cannabis-based medicines according to high pharmaceutical standards. These low doses of THC can produce safe and effective analgesia in patients with chronic pain (Almog et al., 2020).

Theoretical Framework

This study is anchored on the **Theory of Synthesis** by Turner (1990), involves pulling together existing theories and extracting and synthesizing key

aspects to produce robust theory that has relevance to the world outside sociology. Synthesizing theory involves collation, evaluation, and the process of combining ideas for practical use. The synthesis consisted of three stages: synthesis preparation, wherein parts of relevant theories were extracted and summarized; synthesis, which involved comparing theories for points of convergence and divergence and bringing together those points that converge; and synthesis refinement whereby the synthesis was interrogated for further theoretical insights. This process has the potential to strengthen theory and make it more robust and accessible for practical application (Pound & Campbell, 2015).

In this study, systematic reviews and meta-analyses have become increasingly important in healthcare settings. Clinicians read them to keep up-to-date with their field and they are often used as a starting point for developing clinical practice guidelines. Specifically in the use of cannabinoid derivatives in pain management. Moreover, the elements of the Population, Intervention, Comparator and Outcome (PICO) framework will be applied to facilitate the search process and structure the systematic review (Gopalakrishnan & Ganeshkumar, 2013).

Conceptual Framework

The researcher conducts a systematic review and meta-analysis on the efficacy and tolerability of Cannabinoids to manage pain. To do this study, the independent variables presented are the different randomized controlled trials on Cannabinoids. The efficacy and tolerability of cannabinoids towards different types of pain according to their origin are compared. Various aspects of pain can change

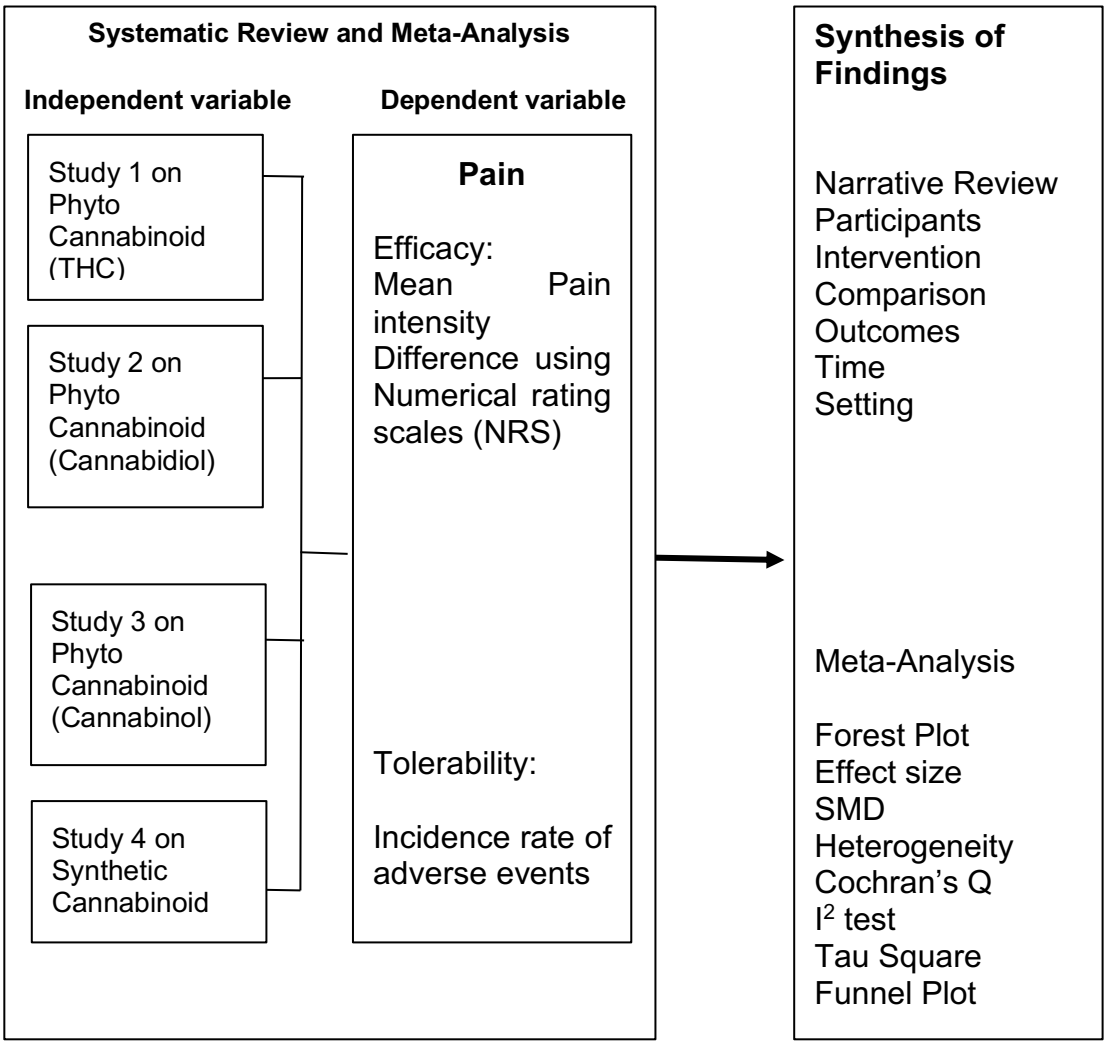


Figure 3. Conceptual Paradigm of the Study

as a result of treatment. The pain caused by malignancy, neuropathic and non-neuropathic, varies in intensity.

It is recommended that two or more different methods be used to evaluate the clinical importance of improving or worsening clinical trial outcome measures for chronic pain. Core outcome measures for chronic pain in clinical trials are employed (Dworkina et al., 2005). Self-report measures provide the ‘gold standard in assessing pain outcomes because they reflect the inherently subjective nature of pain. Still, they should be supplemented by careful assessments of rescue treatments. Under the auspices of the IMMPACT, a consensus that chronic pain clinical trials should assess outcomes representing one of these six core domains: pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, participant disposition like adherence to the treatment regimen and reasons for premature withdrawal from the trial.

This literature review discussed the efficacy of treatment and control using self-reported pain intensity as expressed on a numerical scale. Pain intensity difference is also identified to draw inference on the efficacy aspect of the treatments. Consequently, patients' tolerability on the treatment is mentioned, and adverse events as practiced in epidemiology were also identified.

CHAPTER 2

METHODS

This chapter presents the methodological processes employed in this research. The procedures are outlined in chronological order with specific descriptions and details of the process. It also explains the scope of the study,

Research Design

This research utilized a quantitative study, specifically a systematic review and meta-analysis, to ascertain the effectiveness and tolerability of cannabinoids in pain management. Quantitative design is a study that gives information in numerical formats (Punch & Oancea, 2014). Numbers have much meaning, especially in research investigations (Lhabitant, 2009).

More so, a systematic review is a study that attempts to answer a question by synthesizing the results of primary studies while using strategies to limit bias and random error. These strategies include a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in selecting articles included in the review (Gopalakrishnan & Ganeshkumar, 2013). Research designs and study characteristics are appraised, data are synthesized, and results are interpreted using a predefined systematic approach that adheres to evidence-based methodological principles.

The Preferred Reporting Items of Systematic Reviews Meta-Analysis (PRISMA) guideline was utilized in this review. Thereafter, meta-analysis, was

performed on the outcomes recorded from the different studies to account for effectiveness and tolerability.

Meta-analysis employs statistical techniques to combine the results of the different studies into a single pooled estimate of effect, often given as an odds ratio. The measurable characteristics of the outcomes and features of the quantitative or experimental research studies are analyzed. Afterward, analysis and integration of all the details from both peer-reviewed articles (focusing on clinical trials of similar treatments), a systematic review, and summing up the study results (Cochran, 2002).

A systematic review and meta-analysis research is deemed significant in the study's premises to determine the effectiveness and tolerability of cannabinoids towards pain management among patients. Clinical evidence can be presented compactly; hence, appraisal of benefits can be scientifically executed.

Place of Study

The study was conducted at the University of the Immaculate Conception, Davao City. The University of the Immaculate Conception is a Catholic institution led by the Religious of the Virgin Mary (RVM) in Davao City, Davao Del Sur, Philippines. The university is one of the prestigious schools that offers the course Bachelor of Science in Pharmacy. The study also took place in sites such as library hubs, internet cafes, workplaces, and public places with high-speed Wi-F connections.

Data Sources and Selection

The following databases were used to gather relevant data and studies: PubMed NCBI, ScienceDirect, ClinCal Trials, Research Gate, and Google Scholar. Searches related to “Cannabinoids” and “Pain” were used to supply data. Published papers considered were between January 2015 to March 2022 in the English language with no restrictions on the country in which it has been posted. The researcher included full manuscripts that have been published in the English language within this range to have solid evidence on cannabis-derived drugs in relation to the high technology applied to these studies.

The abstracts were screened when the title of the study appeared relevant. The full texts/manuscripts of the screened studies that initially passed were retrieved for further review. It utilized Medical Subject Headings (MeSH) to search for keyword phrases. For the PubMed Database, the advanced search option was accessed with the filters applied. Screening and Eligibility of the studies were done by filtering them using the inclusion and exclusion criteria presented in the section below. Final studies that were included in the review were downloaded. Only those studies that have measurable outcomes were used for meta-analysis.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria reduce biases and form the boundaries limited to the variables indicated for the study. The inclusion criteria are the primary tool to filter, tailor and identify the most appropriate literature, research studies, and specific studies to be included in this systematic review and further meta-analysis. Further, the inclusion criteria ensure that the outcomes of the study

do not deviate from its goals. It can even help prevent biases in the selection of studies. Studies were considered eligible for complete manuscript data extraction if the study meets all the following criteria: study design follows a randomized, double-blinded, placebo-controlled clinical trial, ambulatory, admitted, or in hospice patients of all ages and races that suffer from pain either acute, or chronic caused by either malignancy, neuropathic or non-neuropathic, receives cannabinoid integrated medicines in different dosage forms and preparations, outcomes, and mean pain using numerical rating scales (NRS) and incidence of adverse events.

The exclusion criteria should also be set because it identifies studies and outcomes that prevent them from achieving the study's primary goal. Other research designs, apart from those given above, were excluded. Studies done and published before 2015 are excluded. Cannabinoids used for recreational were excluded. The visual analog scale for pain intensity recording was excluded as it can produce less efficient results.

Data Extraction

The researcher utilized a data extraction form. The data extraction form contains the following fields: Title of study, authors, year published, study design details, population, intervention details, comparison, and outcomes. This step was done to retrieve data out of data sources for further data processing. Specifically the following search query were used: cannabinoids FOR pain, clinical trials ON cannabinoids.

The data collection process began as soon as the research study was approved by the University's Research Ethics Committee (REC). The researcher starts by signing in or creating an account with the specified databases used for the study. Using the advanced search options and the key terms provided by the study, the researcher independently screened the results of each of the respective databases. The screening of titles was based on the titles' eligibility and the objectives of the studies. Further screening was employed to narrow down other studies specified on the eligibility criteria proposed by the research study. Once eligible studies have been included, further differentiation of the results, study characteristics, interventions employed, and outcome level assessments were analyzed following the study's objectives. They finally led to the qualitative and quantitative interpretation of the studies using data synthesis and analysis methods.

Quality Assessment

Quality assessment tools include the relevance of the research question, appropriateness of data, fitness of eligibility criteria, accessibility of online literature search, and in-depth review in the determination of included and excluded. However, there is no official and best-standardized tool for assessing the quality of studies. Hence, quality assessment tools for systematic review and meta-analysis were used to examine the quality of studies. Consequently, each included study was appraised for internal validity (study quality assessment) using a standardized approach for rating the quality of the individual studies. This process was done by two independent internal reviewers and one external reviewer,

appraising every study for internal validity. These multiple reviewers work independently and have a conference to process and resolve any reviewer disagreements.

The Jadad score is often used to assess the methodological quality of controlled trials. Studies were scored according to three key methodological features of clinical trials, specifically randomization, masking, and accountability of all patients, including withdrawals (Jadad et al., 1996). It is a procedure to assess the methodological quality of clinical trials independently. One point is added for a “yes” answer to each of the first five items, and one point is subtracted for a “yes” answer to either of the last two items for an overall score from 0–5.

Data Synthesis and Analysis

Qualitative Synthesis

The study utilized the PICO Analysis. Initially, the studies were tabulated to see if they had an excellent electronic source. Then, they were inspected to fit the inclusion criteria devised by the researchers. A flow diagram was created to show the process of selecting and excluding studies until all criteria were inspected. After, the remaining studies were tabulated again. This time, the data that were tabulated were from the Data Extraction section. The narrative synthesis followed after. The narrative synthesis was broken down into two sections. The first section was the organization of the description of the studies into logical categories, such as where the study was conducted, the background of the participants, the nature of the intervention, and the relevance of outcomes. The findings are synthesized across all included studies (Pettigrew & Roberts, 2006).

Quantitative Synthesis

Mean Difference and Standardized Mean Difference. This outcome is a continuous type which is looking at results on a spectrum or a range. Mean difference is direct comparison of mean values between two groups. Each of this group should be using the same unit of measurement. Such as in this case, the two treatment arm measures pain using the same instrument generating same unit. The difference of the posttreatment mean pain intensity was subtracted with the baseline or pretest mean pain intensity of treatment group, generating the mean difference for each treatment arm. The expected mean difference in pain carries negative results indicating a decrease in pain intensity by the patients. Thereafter, the mean value of cannabinoid group was subtracted with the mean value of the placebo group to get the mean difference for every included studies. The significance in the difference generated is based on the p-value generated after doing meta-analysis (Andrade, 2020).

Risk and Risk Ratio. For a randomized controlled clinical trial comprising a treatment group and a control group. An inquiry to know how many patients experienced some event during the study period, the results from such a study can be categorized in a figure below (Schwarzer et al., 2015).

	Event	**No Event**	
Treatment	a	b	n_{treat}
Control	c	d	n_{control}
	n_E	$n_{\neg E}$	

Figure 4. Risk Computation

Based on this data, the risk of experiencing events during the study period for both the treatment group and control group can be calculated. Divide the number of people experiencing in one group by the total sample size of that group.

According to the Center for Disease Control, a risk ratio (RR), compares the risk of a health event among one group with the risk among another group. It does so by dividing the risk (incidence proportion, attack rate) in group one by the risk in group two. The two groups are typically differentiated by such demographic factors or by exposure to a suspected risk factor. Often, the group of primary interest is labeled the exposed group, and the comparison group is labeled the unexposed group. A risk ratio can never be negative. Risk ratios are often transformed into the log-risk ratio before pooling.

A risk ratio of 1.0 indicates identical risk among the two groups. A risk ratio greater than 1.0 indicates an increased risk for the group in the numerator, usually the exposed group. A risk ratio less than 1.0 indicates a decreased risk for the exposed group, indicating that perhaps exposure actually protects against disease occurrence.

Forest Plot and Effect Measure. The study utilizes a Forest Plot to quantify the odds ratio and illustrate the strength of the studies. There are two meta-analyses to perform, for the evaluation of the efficacy of treatment for pain management and for the evaluation of tolerability of patients to the treatment. Efficacy effect measure is mean difference and standard mean difference, a continuous measure. While the tolerability effect measure is expressed in binomial, the risk ratio measure.

Heterogeneity Q and I-squared Tests. Heterogeneity is used to describe important differences in studies included in a meta-analysis that may make it inappropriate to combine the studies. Statistical heterogeneity describes the degree of variation in the effect estimates from a set of studies; it is assessed quantitatively. The two most common methods used to assess statistical heterogeneity are the Q test (also known as the X^2 or chi-square test) or I^2 test. The research examined studies to determine its heterogeneity. The Cochrane Q and the I^2 were used to evaluate the heterogeneity of studies (Borenstein et al., 2018).

Random Effect Model. When there is heterogeneity that cannot readily be explained, one analytical approach is to incorporate it into a random-effects model. A random-effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical. The model represents our lack of knowledge on intervention effects differ by considering the differences as if they were random. The center of this distribution describes the average of the effects, while its width describes the degree of heterogeneity. The random-effects pooled estimate only estimate the average treatment effect if the biases are symmetrically distributed, leading to a mixture of over- and under-estimates of effect. The random-effects estimate and its confidence interval address the question ‘what is the average intervention effect?’. For any particular set of studies in which heterogeneity is present, a confidence interval around the random-effects pooled estimate is wider than a confidence interval around a fixed-effect pooled estimate (Higgins, 2022). This will happen if the I^2 statistic is greater than zero.

A random-effects model was used to combine studies showing heterogeneity of Cochrane Q P<0.10 and I^2>50. According to Cochrane, the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows: 0 percent to 40 percent: might not be important; 30 percent to 60 percent: may represent moderate heterogeneity; 50 percent to 90 percent: may represent substantial heterogeneity; 75 percent to 100 percent: considerable heterogeneity. The importance of the observed value of I^2 depends on (i) magnitude and direction of effects (ii) strength of evidence for heterogeneity.

Funnel Plot and Publication Bias. Publication bias is a term used when studies with positive results have a higher likelihood of being published, being published rapidly, being published in higher impact journals, being published in English, being published more than once, or being cited by others. Publication bias can be linked to favorable or unfavorable treatment of research findings due to investigators, editors, industry, commercial interests, or peer reviewers. To minimize the potential for publication bias, the research includes conducting a comprehensive literature search that includes the strategies presented above.

A funnel plot–a scatter plot of component studies in a meta-analysis– is a graphical method for detecting publication bias was used. If there is no significant publication bias, the graph looks like a symmetrical inverted funnel.

Ethical Considerations

The researcher guarantees that all ethical considerations are observed throughout the study. Other information is not made available to anyone who is not

directly involved in the study. The researcher ensures that this study is guaranteed to be approved and reviewed by the UIC-REC.

Social Value. The study implies social value in gathering data and information from different studies. The study results provided a better understanding of the medical application of Cannabinoids. Furthermore, it can help the patients and health professionals in the community to know how to utilize Cannabinoids accurately based on evidence gathered over time. The study result helps formulate policies in the country to guide and guard the public.

The Potential Benefits to Society. The researcher includes all possible studies utilizing Cannabinoids. Thus, the study results can guide patients, healthcare professionals, and policymakers on the evidence of Cannabinoids for different types of pain. Through this research, an interest in using cannabinoids can widen the views and insights of the public and interact more with pharmacists to know their options. At the same time, pharmacists become adaptive in fulfilling the needs of the patients when it comes to this controversial drug. The study is beneficial to patients suffering from different types of pain. The information provides patients and caregivers with evidence-based medicine to make informed decisions regarding their disease and medication. This study benefits future researchers and legislators to understand the importance of evidence-based medicine and how it can serve as a foundation in policymaking.

Use of Publicly Available Data. The study observed confidentiality throughout the conduction of the study. This issue covered all information of the participants from various studies that were included. In compliance with the Data

Privacy Act of 2012, the researcher did not trace back the identity from the past studies of the participants to protect their privacy.

Adequacy of Facilities. Since the study is a systematic review and meta-analysis, the researcher utilizes devices in conducting the research process. The databases were accessed by utilizing the account set by the University. Due to the pandemic, the researcher used online databases to search for studies applicable to the study.

Qualification of Researchers. The researcher of the study has finished all curricular requirements for Ph.D. in Pharmacy at the University of Immaculate Conception. The researcher has also conducted research focusing on pharmacy education and practice. The researcher is spearheading a project on Mango Pectin funded by DOST- PCHRD. This research is done through the joint efforts of the researcher, mentored by a seasoned researcher with a factual background in this research design and scope.

Chapter 3

RESULTS AND DISCUSSION

This chapter presents the results, analysis, and interpretation of the research findings based on the review question presented in the first chapter. The section is chronologically arranged according to PRISMA. This chapter reveals the supporting data on the effectiveness and tolerability of cannabinoids in pain management, as shown in the PICO table.

Study Selection

The flowchart for selecting the studies is shown in Figure 4. This review started with 3,692 studies gathered from electronic databases using the initial keywords “Cannabinoids and Pain Management .”The process of elimination began by removing those irrelevant studies. It was found that there were 2990 irrelevant studies and 454 duplicate studies, therefore eliminated. The 2990 studies were mainly about the potential of cannabinoids in general and only included a segment for pain management. Some studies were quantitative and descriptive, measuring knowledge, perception, and acceptance of Health care on the potential utilization of Cannabinoids for pain management.

Another 454 studies were removed from the list because they are duplication studies. Only 248 studies were left for the screening process. The remaining studies had undergone another process of elimination using the inclusion and exclusion criteria. The elimination further identified the details according to the PICO framework. The 238 studies were excluded in the process. The studies excluded at this point did not qualify the criteria provided. Most of the

studies were not clinical trials and hence excluded from the list. Some clinical trials were not randomly done, did not employ Placebo as control and unblinded, and were excluded from the list. Several studies were published before 2015 and hence excluded. Only ten studies proceeded for eligibility assessment. There was one study removed due to poor quality assessment. One study was removed because it was duplicated; the two studies were accessed from different databases. One study was excluded because it artificially induced pain in the participants which is not within the clause of the review. Only seven studies were left and were subjected to systematic review.

Meta-analysis was performed on studies with identical statistical parameters available to identify the efficacy for pain and tolerability of patients to cannabinoids compared to placebo. Upon further review, the seven studies have uniqueness. Hence not all were subjected to meta-analysis. One study did not present the necessary data for pain intensity difference and was excluded from meta-analysis for efficacy outcomes. A different study also did not present the incidence rate of adverse events in their results; instead just enumerated the observed adverse events, hence cannot qualify to be included in the meta-analysis for tolerability outcomes. Overall, there are two sets with six unique studies for two different meta-analyses for efficacy and tolerability outcomes, respectively.

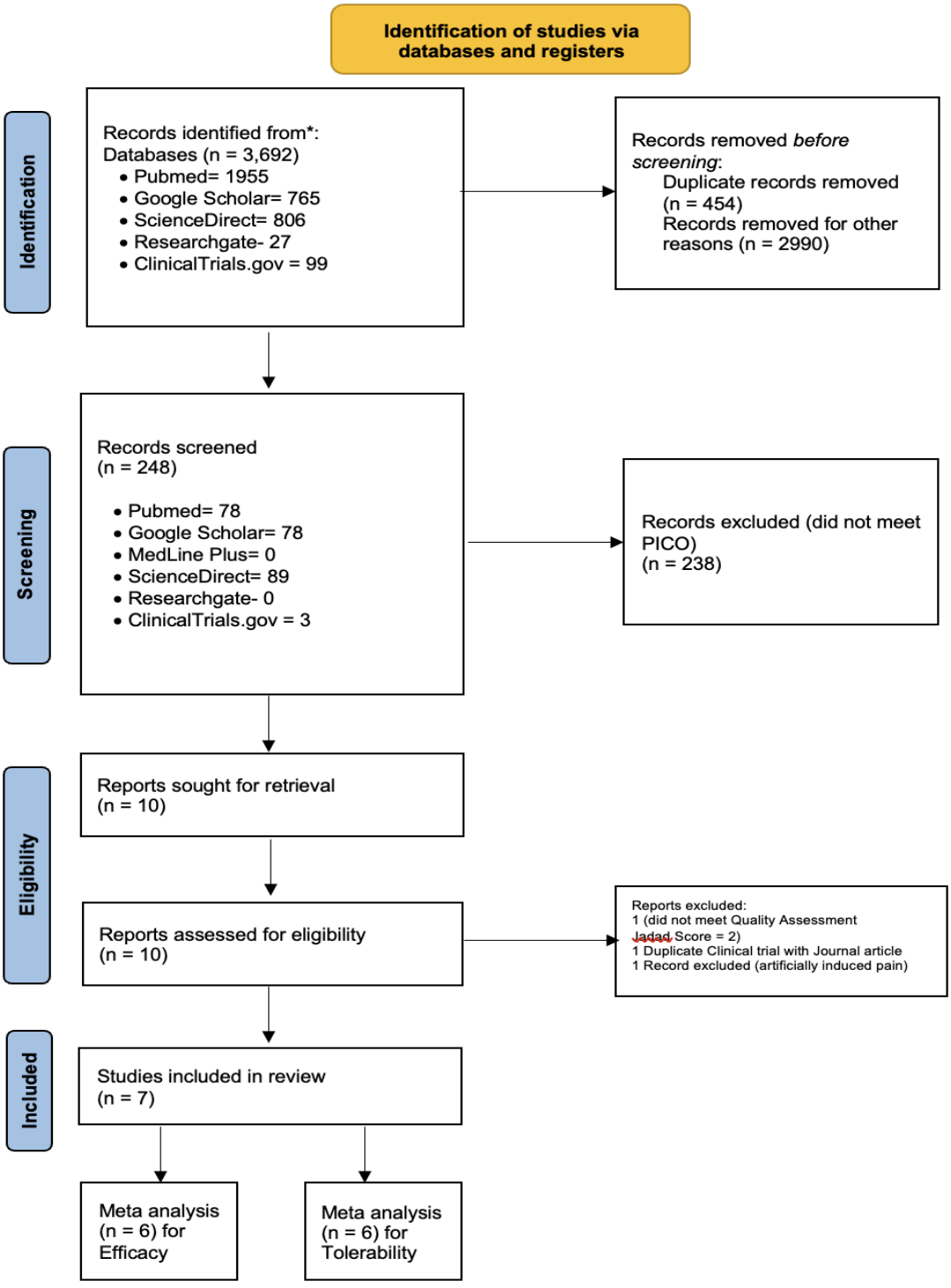


Figure 5. Study Selection Process

Quality assessment

The quality of included studies is determined using the Jadad scoring. Studies with a Jadad score of 2 or less were considered low quality, and those with a Jadad score of 3 or more were considered adequate trial quality (Kjaergard et al., 2001). All of the studies got a score of more than three and are regarded to have adequate trial quality. The seven studies described the method of randomization, implementation of blinding measure, emphasized the use of placebo as a control, and definite description of withdrawals and dropouts.

Features of the Study

Table 1 below presents the seven included studies and their primary features. After reading the contents of each of the seven studies included, general codes were identified and served as features of these studies. There were four features: Author collaboration, Publication dates, Study region, and Study design. Elaboration on the implications of these features is discussed below.

Authorship Collaboration. The titles and corresponding authors are available and presented below. Inclusion criteria allow studies from 2015 to 2022. All studies included were with multiple authors across the country and brought together researchers to accomplish a research output. Hence, it is evident that authorship collaboration is present. In the study of Jones (2018) authorship collaboration is often considered the most verifiable form of research. Research collaboration and shared authorship are linked to globalization and the internationalization of research. International collaboration has been shown to have a positive effect on

the productivity of researchers in terms of the number of publications authored and co-authored, the impact of their research in terms of number of citations, and their research quality in terms of the ranking of the journals of publication.

Table 1
Features of the Included Study

No	Title	Authors	Year	Location	Clinical Trial
1	Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients	Sebastian Schimrigka; Martin Marziniakb; Christine Neubauerc; Eva Maria Kuglerc; G Wernerc	2017	US, EU, Australia	Parallel group trial; Double-blinded Randomized
2	Effects on Spasticity and Neuropathic Pain of an Oral Formulation of Δ9-tetrahydrocannabinol in Patients WithProgressive Multiple Sclerosis	Guido van Ameronge; Kawita Kanhai; Anne Catrien Baakman; Jules Heuberger; Erica Klaassen; Tim L. Beumer; Rob L.M. Strijers; Joep Killestein; Joop van Gerven	2017	Europe	Parallel group trial; Double-blinded Randomized
3	A double blind, randomized, placebo-controlled, parallel group study of Sativex oromucosal spray (Sativex®; Nabiximols) as adjunctive therapy in relieving uncontrolled persistent chronic pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy.	Marie T Fallon; Eberhard Albert Lux; Robert McQuade; Sandro Rossetti; Raymond Sanchez; Wei Sun; Stephen Wright; Aron Lichtman; Elena Kornyeyeva	2017	World wide	Parallel group trial; Double-blinded Randomized

4	Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain	Aron H. Lichtman; Eberhard Albert Lux; Robert McQuade; Sandro Rossetti; Raymond Sanchez; Wei Sun, Stephen Wright; Elena Kornyeyeva; Marie T. Fallon	2018	Europe, US	Parallel group trial; Double-blinded Randomized
5	Tetrahydrocannabinol and cannabidiol oromucosal spray in resistant multiple sclerosis spasticity: consistency of response across subgroups from the SAVANT randomized clinical trial	Sven G Meuth; Thomas Henze; Ute Essner; Christiane Trompke & Carlos Vila Silván	2020	Germany	Parallel group trial; Double-blinded Randomized
6	Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial	Luca Eibach; Simone Scheffel; Madeleine Cardebring; Marie Lettau; M. Özgür Celik; Andreas Morguet; Robert Roehle	2020	Berlin, Germany	Cross over design; Double-blinded Randomized
7	The CANBACK trial a randomised, controlled clinical trial of oral cannabidiol for people presenting to the emergency department with acute low back pain	Bronwyn Bebee; David M Taylor; Elyssia Bourke; Kimberley Pollack; Lian Foster; Michael Ching; Anselm Wong	2021	Melbourne, Australia	Parallel group trial; Double-blinded Randomized

Multilateral collaboration with high-level R&D countries yields the highest values of research impact, although the impact of collaboration with low-level R&D

countries has been optimized over the years. Likewise, scientific collaboration is frequently based on individual initiative, policy actions are required to promote the more heterogeneous types of collaboration (Bordons et al., 2013). Thus, heterogeneity of collaboration directly provides a positive impact on the research output, most definitely in biomedical sciences.

Publication Date. After the screening process, the studies that qualify for the review were published within the last five years (2017 to 2021). Recent research outputs like these studies are expected to be embedded with new technologies and innovations. These studies are potential solutions and can open discussions in elevating best practices in pain management (Foster et al., 2018). The newer the data, the better and more time it is. Though there are cases where the relevance of the data even though it is old, this is usually the case if there is no other literature available to support the research. However, as much as a possible maximum of 5 years old data is observed.

Hence, these included studies can provide effective, promising, or emerging solutions that could offer new directions in pain management through Cannabinoid integrated medicines. In addition, based on the study of Yekkirala et al. (2017) novel analgesic drug development, clinical practice guidelines in the management of patient pharmacotherapy only utilize evidence-based research recently published from the time of implementation. Therefore, these studies are advantageous because of the most significant potential to align practice with the evidence.

Study Region. Seven of these studies were performed in Europe, three of which were participated by patients from the United States of America and Australia. Only one study was conducted worldwide. Generally, the respondents are Caucasians, and the treatment outcomes presented below are limited to this race. Race is an example of an intrinsic ethnic factor. It identifies a subpopulation and may influence the ability to extrapolate clinical data between regions. In this context, Caucasians have a specific genetic profile, genetic polymorphism, body composition, and organ dysfunction notably different from Asians and other races.

In addition, extrinsic ethnic factors are associated with the environment. It is more culturally and behaviorally determined. Caucasians have different social and cultural orientations such as medical practice, diet, tobacco, use of alcohol, exposure to pollution and sunshine, and socioeconomic profile compared to Asians and other races. Medicine's sensitivity to ethnic factors characterizes medicine according to the potential impact of ethnic factors on its pharmacokinetics (PK), pharmacodynamics (PD), and therapeutic effects. This can be useful in determining future directions in studying different populations or locations of study. The impact of ethnic factors on a medicine's effect will vary depending upon the drug's pharmacologic class and indication and the age and gender of the patient (DiPiro, 2020).

In recent decades, global clinical trials have increased because of the need for timely drug approval in multiple countries (Mori & Toyoshima, 2009). In these clinical trials, interethnic differences in PK and PD properties should be considered. Moreover, because inter-ethnic differences in PK properties have

been reported between East Asian and white populations, the clinical trial results of one group cannot be readily extrapolated to the other. It remains unclear whether inter-ethnic differences in PK and PD properties of medications are present among East Asian populations. However, East Asian clinical trials have been effective for some high prevalence diseases. Thus, it may be necessary to clarify ethnic differences in PKs and PDs to facilitate the utilization of clinical trial data across East Asian countries, such as Japan, China, and South Korea (Aoyama et al., 2017).

Cannabinoids possess PK/PD properties that make them sensitive to ethnic factors. Cannabinoids are highly metabolized, have a high likelihood of inappropriate use, and have slow and unpredictable oral absorption. It is best to administer it via inhalation compared to oral administration. Therefore, clinical trials strictly controlled for extrinsic factors such as inter-ethnic differences in the PKs of drugs in terms of the associated intrinsic factors will be beneficial. Hence, more clinical studies on cannabinoids for pain management will be beneficial to have more complete results.

Study Design. There are two significant study designs by which drugs are evaluated in standard PK assays: parallel study and crossover study. This review has gathered six studies that utilized parallel-group, and one used a crossover clinical trial design. Both types of clinical trials are pivotal in the overall drug development process in that they provide primary evidence of safety and efficacy. Six studies used a parallel with two separate treatment arms—the cannabinoids as the intervention arm and placebo as the control arm. According to the National

Institutes of Health (NIH), the parallel study is that randomization is advantageous due to its randomness. This process ensures the accuracy of the results and lowers the risk of bias. The advantage of a parallel design is that it provides the best way to assess the effect of a drug on survival if that is the critical endpoint in its evaluation. One included study utilized a crossover or crossover trial design. In this type of clinical trial study, as discussed in the Cochrane Handbook (2022, only one phase should be included when comparing the outcomes from the parallel study design.

Participants, Intervention, Comparator, and Outcome (PICO)

To establish a well-focused question and identify appropriate resources and search for relevant evidence, Practitioners of Evidence-Based Practice (EBP) use a specialized framework, called PICO, to form the question and facilitate the literature search. The table below displays the PICO elements of the eight included studies.

Study 1. This study was conducted in Europe, the US, and Australia and published in 2017. It employed a randomized, double-blinded, parallel design clinical trial that lasted for 16 weeks. The participants were 18 to 70 years old. There were no relevant differences between the two treatment groups regarding baseline demographic data.

Table 2
Participants-Intervention-Comparator-Outcome (PICO)

Study	Participant	Intervention	Comparator	Outcomes	
				Efficacy	Tolerability
1. Schimrigka et al. (2017)	Adults	Dronabinol	Placebo	Pain Intensity (NRS)	Incidence of Adverse events
2. Ameronge et al. (2017)	Adults	Dronabinol	Placebo	Pain Intensity (NRS)	Incidence of Adverse events
3. Fallon et al.(2017)	Adults	Nabiximols Spray	Placebo	Pain Intensity (NRS)	Incidence of Adverse events
4. Lichtman et al (2018)	Adults	Nabiximols Spray	Placebo	Pain Intensity (NRS)	Incidence of Adverse events
5. Meuth et al. (2020)	Adults	Nabiximols Spray	Placebo	Pain Intensity (NRS)	Adverse events
6. Eibach et al. (2020)	Adults	Cannabidivarin	Placebo	Pain Intensity (NRS)	Incidence of Adverse events
7. Bebee et al (2021)	Adults	Oral Cannabidiol	Placebo	Pain Intensity (NRS)	Incidence of Adverse events

The mean age at randomization was 47.7 ± 9.7 years, and 72.9 percent were female. Patients' mean age during long-term follow-up was 48.4 ± 9.1 years;

the mean NRS at the beginning was 3.4 ± 2.1. During the double-blind period, 39.5 percent of patients in the verum and 44.0 percent in the placebo group took allowed analgesics, most frequently gabapentin (20.8% of patients). In terms of drop-outs, there were nineteen from the treatment and twelve from the placebo control. Lack of compliance is also noted in both arms, two patients from the treatment, and placebo groups.

Likewise, some participants withdrew informed consent, six from the treatment group and seven from the placebo group. The participants in the treatment arm received Dronabinol, a maximum of 15 mg/ day. Mean pain intensity from the baseline to week 16 was recorded and statically treated using a two-sample t-test. The general results revealed 30 percent pain reduction in the treatment arm and 27 percent in the placebo arm. In the double-blind period, the proportion of patients experiencing Adverse events was higher. The proportion of patients experiencing Serious Adverse events was low. Overall, the number of AEs and ARs decreased over time with no time dependency for SAEs and SARs occurrence. Most patients reported no withdrawal reactions after cessation of study medication. Mild signs of drug dependency were documented only for one patient. No patient showed any sign of drug abuse.

Study 2. Studied done in Europe are randomized double-blinded placebo-controlled parallel design clinical trial (Ameronge et al., 2017). Twenty-four patients 18 years or older with a diagnosis of progressive; primary or secondary, multiple sclerosis experience pain. The study's last Current use of Δ9-THC was exclusionary, as confirmed per urine drug screen. All patients provided written

informed consent before participation. The intervention given to the participants was Δ9-tetrahydrocannabinol (ECP002A). Each of the two visits in the challenge phase consisted of an up-titration of three consecutive drug administrations with a 100-minute interval in ascending order. If well tolerated, the three-dose levels were predetermined to be three, five, and eight mg, leading to a total daily dose of 16 mg, based on the previous study's PK and PD findings. Between the two visits was a washout period of seven to 14 days. Predetermined daily dose divided over three intakes. After two weeks of treatment, the dose for each patient was evaluated and increased when considered appropriate. The study only provided limited information for efficacy outcomes; hence this study was not utilized for meta-analysis for efficacy. On the other hand, it has quantifiable results for adverse events that qualify for meta-analysis.

Study 3. In the study of Fallon et al. (2017), Sativex was the cannabinoid used as an intervention for participants with an advanced incurable stage of cancer. This clinical trial was done worldwide on patients ≥ 18 years of age with a clinical diagnosis of cancer-related pain unalleviated by an optimized maintenance dose of Step three opioid therapy. To be eligible, patients also had to fulfill the following criteria on each of three consecutive days during the screening period: ≤ four opioid breakthrough analgesic episodes per day (averaged over the three days), a stable maintenance opioid therapy dose, average pain ≥ 4 and ≤ 8 on a zero–ten NRS and average pain scores on the NRS that did not change by more than two points from the beginning to end of screening (i.e., no more than a two-

point difference between the highest and lowest scores, with all scores remaining between four and eight).

Key exclusion criteria in study one included baseline use of morphine at >500mg morphine equivalents/day, current use of more than one type of breakthrough opioid analgesic, planned clinical interventions that would affect pain, and any history of schizophrenia or substance abuse, including recreational use of cannabis product. Following the ratio of 1:1 to Sativex or placebo in a double-blind fashion, Patients then received study treatments at their self-titrated doses for five weeks. Two weeks after the end of treatment, patients were contacted by phone for follow-up safety evaluations. Nabiximols were self-administered by participants as a 100 µL oromucosal spray in the morning and evening, for five weeks, at the same level of dosing attained during the last four days of the single-blind period; however, the number of sprays could be decreased based on tolerability throughout the study. Nabiximols oromucosal spray contained THC (27 mg/mL):CBD (25 mg/mL), in ethanol: propylene glycol (50:50) excipients, with peppermint oil flavoring. Each 100 µL actuation delivered 2.7 mg THC and 2.5 mg CBD.

Participants indicated the level of pain experienced in the last 24 hours on an 11-point NRS, where a score of zero indicated "no pain," and a score of ten indicated "pain as bad as you can imagine." Change in mean NRS average pain was calculated as end of treatment NRS average pain score - randomization baseline NRS average pain score. The most common adverse event in the Sativex-treated group was somnolence, which occurred in six (5.8%) Sativex-

treated patients; treatment-related somnolence was not observed in placebo-treated patients. All other adverse events occurred at an incidence of < five percent within either treatment group. Across both studies, neoplasm progression (all cases unrelated to study treatment) was the most common adverse event.

Study 4. This study is authored by Lichtman and was published last 2018. As the title presents, it is a double-blinded randomized placebo-controlled parallel design clinical trial on Nabiximols. In this study, the participants had advanced cancer for which there was no known curative therapy. The participant had a clinical diagnosis of cancer-related pain, which was not wholly alleviated with their current optimized opioid treatment. Qualifying participants entered the study at screening and commenced a five to 14-day eligibility period. During this period, eligible participants had three consecutive days where pain severity remained within defined parameters, break-through opioid usage had not exceeded an average of four episodes per day, and maintenance opioid medication and dose had not changed.

Eligible participants returned for randomization on Day one and were randomized to either the nabiximols or placebo treatment arm using a 1:1 allocation ratio. After the five-week treatment period ended, participants were offered the option of entering an open-label extension (OLE) study; a safety follow-up visit (up to Day 43) was not required if the participant entered the OLE on Day 36. Nabiximols were self-administered by participants as a 100 microliter (μL) oromucosal spray in the morning and evening, up to a maximum of ten sprays per day for five weeks. Nabiximols oromucosal spray contained delta-9-

tetrahydrocannabinol (THC) (27 milligram [mg]/milliliter [mL]):cannabidiol (CBD) (25 mg/mL), in ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavoring. Each 100 µL actuation delivered 2.7 mg THC and 2.5 mg CBD. Participants indicated the level of pain in the last 24 hours on an 11-point NRS, where a score of 0 was "no pain," and ten was "pain as bad as you can imagine." Baseline = mean score from the first day of the three-day eligibility period to the day before the first dose of the study drug. End of treatment = means score over the last up to seven days to the final pain score at the end of Treatment or up until Day 35, whichever is earlier, or the final score available (prematurely terminated). Furthermore, regarding the tolerability outcomes, 144 of 199 patients (72.4 percent) on nabiximols and 130 of 198 (65.7%) on placebo developed one or more Adverse events.

The most common in both groups was neoplasm progression, followed by nausea, dizziness, vomiting, and decreased appetite. Overall, 39 patients (19.5%) experienced an event that was mild in severity, 57 (28.6 %) experienced a moderate event, and 48 (24.1%) experienced a severe event. Treatment-related adverse events occurred in 70 of 199 patients (35.2%) in the nabiximols group and 41 of 198 (20.7%) in the placebo group. The most common were nausea and dizziness. In total, 27 patients (13.6%) died in each treatment group. No death was considered treatment-related. Forty-nine of the fifty-four deaths were attributed to underlying cancer. Two of the remaining five deaths occurred in the nabiximols group, including a patient with metastatic cervical cancer who developed

pancytopenia and a patient with metastatic bone cancer who suffered from a pulmonary embolism.

Study 5. In the study of Meuth et al. (2020), the intervention was the same in several studies, the Nabiximols (Sativex). This clinical trial is a randomized, double-blinded parallel design on adult patients who experiences chronic pain related to Multiple sclerosis. The population mean (SD) age was 51.3 (10.2) years. At baseline, the study population had moderate to a high disability, moderate to severe MS spasticity, and moderate pain (mean [SD] 0-10 NRS score of 5.5 [1.9]). At the baseline of the 12-week double-blind treatment phase, 84.9 percent of patients received baclofen, 31.1 percent received tizanidine, and 16.0 percent received combination therapy. Treatment was completed by 94.3 percent of randomized patients (50/53) in the THC: CBD oromucosal spray (nabiximols) group and by 88.8 percent of randomized patients (46/53) in the placebo group.

Withdrawal of consent (n = 4) was the main reason for treatment discontinuation during the double-blind phase. Results of post hoc analyses of mean pain (0−10 NRS) scores were reduced with THC: CBD oromucosal spray (nabiximols) compared with placebo in patients. Mean pain NRS scores were reduced with THC: CBD oromucosal spray (nabiximols) compared with placebo patients with spasticity 0-10 NRS scores of ≤ six or > six at randomization, with statistically significant differences in the spasticity NRS score > six subgroups. In the spasticity NRS score ≤ six subgroups, mean (SD) changes in pain zero-ten NRS scores between randomization and week 12 of treatment were -2.36 (1.51) with THC: CBD spray (nabiximols) and -2.07 (1.54) with placebo (p = 0.4979).

In addition, mean pain NRS scores were reduced significantly with THC: CBD oromucosal spray (nabiximols) compared with placebo irrespective of MS spasticity duration. In the patient subgroup with spasticity duration ≤ five years, mean (SD) changes in pain 0-10 NRS scores between randomization and week 12 of treatment were -2.29 (2.18) with THC:CBD spray (nabiximols) and -1.52 (2.22) with placebo ($p = 0.0307$). Corresponding values in the patient subgroup with spasticity duration > five years were -3.48 (2.47) and -2.22 (2.07), respectively ($p = 0.0108$). In each spasticity duration subgroup, differences between active treatment and placebo were also significant at weeks four and eight. For the adverse events, the study shortly mentioned few adverse events such as neurological in nature. No incidence rates and any quantifiable data useful to run the meta-analysis for tolerability outcomes.

Study 6. This study by Eibach et al. (2020) is considered the unique addition that sets this research different from the other SRMAs done on cannabinoids. This clinical trial used the novel drug considered to be a new molecular entity synthesized from the cannabis plant. Cannabidivarin, also known as cannabidiol or CBDV, is a non-psychoactive cannabinoid found within medical cannabis. This clinical trial is given to HIV patients who experience chronic debilitating pain. The study lasted for two years. Before inclusion, subjects were screened for age (18–65 years), vital signs, and pain intensity (≥ 4 on an 11-point NRS. The diagnosis of HIV- associated sensory neuropathy was confirmed by a clinician based on patient history, the douleur neuropathique four interview (DN4i), and the clinical HIV-associated Neuropathy Tool. Exclusion criteria were

pregnancy and lactation, primary psychiatric conditions, severe diseases of the central nervous system, hepatic, renal, or cardiovascular diseases, or use of conventional cannabinoids (CBS), examined by a blood test.

The use of concomitant analgesics (including antidepressants and anticonvulsants) as needed was permitted throughout the study. Standard laboratory values (complete blood count, liver function tests, electrolytes, glucose, urea, cholesterol, creatinine, creatinine kinase, protein, and international normalized ratio) were recorded during the screening and the trial. The active agent and placebo were dissolved in sesame oil and identically appearing and tasting solutions. The Investigational Medical Products were packaged in amber glass bottles by GW Pharmaceuticals. All bottles were subject-specific and marked with the patient ID. The bottles with active agents contained 50 mg CBDV/mL. Patients were instructed to use eight ml of the solution orally every morning at 9 am, corresponding to 400 mg CBDV in the verum treatment phase. The dose was chosen based on preclinical and clinical phase one studies, showing that daily doses between 200 and 800 mg were well-tolerated. The primary outcome was pain intensity measured thrice daily (8:30 am, 1:00 pm, and 7:00 pm) by an 11-point NRS (0 = no pain to 10 = worst pain imaginable), as documented in the patient diary. The arithmetic mean of the three NRS scores was determined for each day.

According to several previous studies on neuropathic pain, a decrease of mean NRS values by at least 20 percent between the last day of baseline measurement and the last day of treatment was defined as a clinically relevant

effect (responder). Thirty-one patients (91.2 %) experienced at least one adverse event (AE) during CBDV treatment, and 27 patients (79.4 %) had at least one AE during placebo. During each treatment (CBDV or placebo), nine patients (26.5 %) experienced an AE that was considered related to the study medication. One serious AE (acute myocardial infarction) was recorded during CBDV treatment but was judged unrelated to study medication. This patient (male, 62 years) had the following cardiovascular risk factors: history of arterial hypertension, transient ischemic attack, pulmonary embolism, and factor-V-Leiden mutation. The most common AEs were diarrhea and dry mouth (3 cases during each treatment). The incidence of AEs was similar in both treatment phases. All AEs were of low or moderate severity; one patient withdrew from study participation due to an AE (cough) during CBDV treatment. This issue was considered related to treatment. No clinically relevant or medication-related changes in laboratory values were noted.

Study 7. The most recently published study by Bebee et al. (2021) on a clinical trial employs oral cannabidiol for patients with acute low back pain. It includes ages 18 years or older who presented with acute non-traumatic low back pain of fewer than 30 days. This definition included people with histories of low back pain. People who reported using cannabis or CBD in the preceding seven days, those with abnormal neurological examination findings (apart from subjective sensory changes), fever (exceeding 37.6°C), a history of malignancy, or a non-musculoskeletal cause of back pain, and women who were pregnant (urinary β-

human chorionic gonadotropin testing of all women under 60 years of age) were excluded.

Patients received either the placebo (control group) or CBD (intervention group). CBD (> 99.9 percent synthetic) and placebo were purchased as color-matched medications from GD Pharma (South Australia). The hospital pharmacy supplied 400 mg CBD in 4 mL medium-chain triglyceride [MCT] oil) and placebo (4 mL MCT oil) as single oral syringe doses. The selection of the 400 mg dose was based on safety and toxicology data for CBD in humans and on earlier studies of the therapeutic effects of CBD in children and adults. In one investigation, the effects of single oral 400 mg or 800 mg CBD doses administered together with intravenous fentanyl were assessed. The authors defined a two-point difference between mean pain scores for the two groups two hours after administration as clinically significant. In order to detect a two-point difference in mean pain scores, the researchers calculated that 47 patients in each group were required ($\alpha = 0.05$, 2-sided; power, 0.9).

The primary outcome of our intention-to-treat analysis was a change in numerical pain scores. The statistical significance of differences between groups was assessed in unpaired t-tests. Between-group differences in non-parametric variables were also analyzed. Pain scores across time (every 30 minutes for two hours) were assessed by two-way analysis of variance (ANOVA) by time after administration. Mean pain scores at two hours were similar for the CBD (6.2 points; 95% CI, 5.5–6.9 points) and placebo groups (5.8 points; 95% CI, 5.1–6.6 points; absolute difference, –0.3 points; 95% CI, –1.3 to 0.6 points). The median length of

stay was 9.0 hours (IQR, 7.4–12 hours) for the CBD group and 8.5 hours (IQR, 6.5–21 hours) for the placebo group. Oxycodone use during the four hours preceding and the four hours after receiving CBD or placebo was similar for the two groups, as were reported side effects. The adverse events are observed in both treatment arms: sedation, diarrhea, nausea, vomiting, headache and lightheadedness, dry throat, and constipation.

Similarities and Differences Across Included Studies

After presenting the pertinent information and background within the scope of PICO for every studies, this next section presents the similarities and difference within the scope of PICO across all the included studies.

Participants. After the screening process, all of the seven studies with similar participants were included, among other considerations. The eight studies are interested in adult patients aged 18 years old and above with different types of pain.

Table 3
Participants of the Included studies

Study	Age	Number of Patients	Type of Pain
1.Schimrigka et al. (2017)	18-70 years old	Total: 240 Intervention: 124 Placebo: 116	Neuropathic Pain
2.Ameronge et al. (2017)	18 years old and above	Total: 24 Intervention: 12 Placebo: 12	Neuropathic Pain-MS
3.Fallon et al.(2017)	18 years old and above	Total: 216 Intervention: 108 Placebo: 108	Cancer Pain
4.Lichtman et al (2018)	18 years old and above	Total: 370 Intervention: 190 Placebo: 190	Cancer Pain
5.Meuth et al. (2020)	18 years old and above	Total:106 Intervention:53 Placebo: 53	Chronic Neuropathic Pain
6.Eibach et al. (2020)	18-65 years old	Total: 32 Intervention:16 Placebo: 16	Chronic Pain, HIV
7.Bebee et al (2021)	18 years old and above	Total:100 Intervention: 50 Placebo: 50	Acute Pain

Regarding the sample size, five of the studies have more than 100 total patients in both treatment arms, and three studies have below 50 patients in both treatment arms. Patients in the six studies complain about chronic pain due to neuropathic origin and malignancy. There is one study interested in patients with acute pain. General information on the scope of participants gives the public, the researchers, and the clinician more understanding that cannabinoids are safe to

be administered and studied within this age range. The studies are well accepted, as manifested by the large sample size of participants.

Interventions of the Included Studies. This review is highly focused on including studies on Cannabinoids for pain management. Any dosage form, preparation, and strength are included. The table below displays the intervention profile given to the patients in the included studies. Nabiximols (Sativex), a synthetic cannabinoid, are common in three included studies, following the same route of administration, dosage, and frequency for at least five weeks. Dronabinol was studied in two studies; cannabidiol and the newly discovered cannabidivarin are also included in the interventions under observation.

*Nabiximols (Sativex)***.** According to NIH National Cancer Institute, Nabiximols is an herbal preparation containing a defined quantity of specific cannabinoids formulated for oromucosal spray administration with potential analgesic activity. Nabiximols contain a standardized extract of tetrahydrocannabinol, the non-psychoactive cannabinoid cannabidiol, and other minor cannabinoids, flavonoids, and terpenes from two cannabis plant varieties.

Table 4
Interventions of the Included studies

No.	Name	Route of Administration and Strength	Dosage and frequency	Treatment Duration
1.Schimrigka et al. (2017)	Dronabinol	Oral Capsule 2.5, 5, 10 mg	12.7+ 2.9 mg; maximum of 15/day	16 weeks
2.Ameronge et al. (2017)	Dronabinol	Oral Capsule 2.5, 5, 10 mg	16 mg/ day in 3 divided dose	4 week
3.Fallon et al.(2017)	Nabiximols (Sativex)	Oral Spray ((2.7mgTHC/ 2.5mgCBD)	10 sprays of 100 µL spray BID x 5 weeks.	5 weeks
4.Lichtman et al (2018)	Nabiximols (Sativex)	Oral Spray ((2.7mgTHC/ 2.5mgCBD)	10 sprays of 100 µL spray BID x 5 weeks.	5 weeks
5.Meuth et al. (2020)	Nabiximols (Sativex)	Oral Spray ((2.7mgTHC/ 2.5mgCBD	10 sprays of 100 µL spray BID	12 weeks
6. Eibach et al. (2020)	Cannabidivarin 50 mg/mL.	Oral solution (50 mg/ml)	400 mg (8 mL) orally every morning at 9 am	4 weeks
7.Bebee et al (2021)	Oral Cannabidiol (Epidiolex)	Oral solution 100 mg/ ml	400 mg dose (4ml)	12 months

Cannabinoids interact with cannabinoid 1 (CB1) receptors in the central nervous system, resulting in analgesic, euphoric, and anticonvulsive effects. Nabiximols (Sativex) is the first cannabis-based medicine to be licensed in the UK (D'hooghe et al., 2021). As this cannabinoid oromucosal spray is classified as a controlled substance in the European Union, its prescription and distribution must comply with narcotics legislation. Common side effects include dizziness, drowsiness, constipation or diarrhea, fatigue, memory or concentration problems,

and a dry mouth or changed sense of taste. These side effects are more likely when you start treatment and usually wear off within a few days. Sativex is not recommended for pregnant women and people under 18 years old. People with psychotic problems should not take the drug (Flachenecker et al., 2014). Based on the three clinical trials that studied Nabiximols, the mean pain intensity decrease was at least two numerical scales lesser than the baseline mean pain intensity. This signifies effective clinical pain management provided by drugs to these patients.

Dronabinol. According to the National Library of Medicine, Dronabinol (Marinol) is an isomer of tetrahydrocannabinol (THC), the primary and most active isomer in the Cannabis sativa L. plant, with potential anti-emetic, analgesic, and appetite-stimulating activities. This agent induces analgesia. It belongs to a subclass of analgesic agents that typically do not bind to opioid receptors and are not addictive. Along with its needed effects, dronabinol may cause some unwanted effects. Based on the Drugs.com database, here are some of the adverse effects: Changes in mood, confusion, delusions, fast or pounding heartbeat, feelings of unreality, loss of memory, mental depression, nervousness or anxiety, problems with memory, and hallucinations. The two clinical trials included in this review provided contradictory outcomes. In the study of Schimrigka et al. (2017), the mean pain intensity difference decreased to four numerical scales. On the other hand, in the study of Ameronge et al. (2017), there is an increase in pain intensity post-treatment of Dronabinol and even in the placebo control. However, with this

clinical information, more trials should be conducted for dronabinol for pain management to generate more concrete data.

Cannabidiol. Only one of the clinical trials included in this review has studied this cannabinoid. As published in the database of PubChem, cannabidiol is a phytocannabinoid derived from Cannabis species, devoid of psychoactive activity, with analgesic, anti-inflammatory, antineoplastic and chemopreventive activities. Cannabidiol, or CBD, is one of at least 85 active cannabinoids identified within the Cannabis plant. It is a major phytocannabinoid, accounting for up to 40 percent of the Cannabis plant's extract, that binds to various physiological targets of the endocannabinoid system within the body.

In particular, CBD has shown promise as an analgesic, anticonvulsant, muscle relaxant, anxiolytic, antipsychotic, neuroprotective, anti-inflammatory, and antioxidant, among other currently investigated uses. The analgesic effect of CBD is mediated through the binding of this agent to and activation of CB1 (PubChem Compound Summary for CID 644019, Cannabidiol*., 2022*). The exact medical implications are currently being investigated, and CBD has shown promise as a therapeutic and pharmaceutical drug target. In the mean pain intensity difference in the study of Bebee et al. (2021), the placebo has a more significant pain intensity difference than the treatment arm. This clinical trial also is unique from the other included studies because its studies on acute pain experiences and alleviation were observed within 24 hours. In this sense, cannabinoids may not manage acute pain very well. It needs to be studied more; it seems to need a longer duration of treatment to have clinically significant pain intensity reduction.

*Cannabidivarin***.** This drug is a chemical in the Cannabis sativa plant. Cannabidivarin, also known as cannabidivarol or CBDV, is a non-psychoactive cannabinoid. It is similar to cannabidiol (CBD). Like CBD, cannabidivarin does not affect thinking (PubChem Compound Summary for CID 11601669, Cannabidivarin, 2022). Early research suggests that cannabidivarin might make specific nerve cells less active. These nerve cells are involved in swelling (inflammation); by making these cells less active, cannabidivarin might improve swelling and pain. It is possibly safe to take cannabidivarin at a dose of up to 1600 mg daily for up to 8 weeks. It might cause side effects such as diarrhea, dizziness, headache, sleepiness, and nausea.

There is not enough reliable information to know if cannabidivarin is safe when used in larger doses or for more than eight weeks (Eibach et al., 2020). Cannabidivarin does not currently have any FDA or Health Canada-approved indications; however, in October 2017, CBDV was given the orphan designation by the European Medicines Agency for use in Rett Syndrome and again in February 2018 for treatment of Fragile X Syndrome (“Science Medicines Health,” 2018). Since this is a newly discovered cannabinoid medicine, its inclusion in the array of interventions reviewed in this research provides distinction from other existing systematic reviews done with cannabinoid integrated medicines. The pain intensity reduction recorded with cannabidivarin can be considered clinically significant and shows potential in pain management. Further studies on dose adjustment may yield optimum outcomes.

Comparator of the Included Studies

For this review, a Placebo or Placebo-controlled study, is the chosen comparator that measured against the different cannabinoid interventions. Placebo is regarded as a true control (Melnyk & Fineout-Overholt, 2005).

Table 5
Comparator of the Included studies

No.	Placebo Component
1.Schimrigka et al. (2017)	No details provided
2.Ameronge et al. (2017)	Matching placebo tablets were man ufactured and provided under the responsibility of Echo Pharmaceuticals B.V.
3.Fallon et al.(2017)	Placebo oromucosal spray contained ethanol:propylene glycol (50:50) excipients, with peppermint oil (0.05 percent) flavoring and colorings.
4.Lichtman et al (2018)	No details provided
5.Meuth et al. (2020)	No details provided
6.Eibach et al. (2020)	The active agent and placebo, both dissolved in sesame oil, were identically appearing and tasting solutions. The Investigational Medical Products was packaged in amber-glass bottles by GW Pharmaceuticals. All bottles were subject-specific and marked with the patient ID.
7.Bebee et al (2021)	Placebo were purchased as colour-matched medications from GD Pharma (South Australia).

The researchers of these studies made sure that the excipients of the intervention and placebo drug are identical to eliminate variance in response. A placebo is an inactive substance that looks and tastes like the drug being tested but does not affect the disease the new drug is intended to treat. By randomly

assigning subjects to active treatment and placebo groups, diversity is spread equally between the groups. Placebo-controlled clinical trials are the fastest way to develop new treatments. A placebo-controlled trial is a trial in which there are two (or more) groups. Researchers use placebos during studies to help them understand what effect a new drug or other treatment might have on a particular condition. Researchers then compare the effects of the drug and the placebo on the people in the study. That way, they can determine the new drug's effectiveness and check for side effects.

The placebo effect can occur when the treatment is helping, when it is doing nothing, or when it is harming us. The double-blind, placebo-controlled trial is considered the "gold standard" for clinical trials because it has the best chance of determining whether active treatment is effective (Möller, 2011). Sometimes a person can get a response to a placebo. The response can be positive or negative. For instance, the person's symptoms may improve. Alternatively, the person may have what appears to be side effects from the treatment. These responses are known as the "placebo effect." There are some conditions where a placebo can produce results even when people know they are taking a placebo. Studies show that placebos can affect conditions such as depression, pain, sleep disorders, irritable bowel syndrome, and menopause (Saling, 2022).

Only with placebo-controlled trials could these two treatments be ruled out as ineffective, saving patients from taking medicines that offer no benefit and could even be dangerous. An important point to remember is that experimental drugs are indeed experimental. That means that the drug can have a positive, no effect

at all, or be detrimental. It is sometimes challenging to remember that a patient on a placebo may be getting better treatment than someone on active medication. A trial with a negative result is very disappointing to both participants and study organizers. However, every trial teaches us something valuable and makes subsequent trials more likely to succeed. The disappointment of negative trial results only strengthens the commitment to finding genuinely beneficial treatments.

Outcomes of the Included Studies

Specific outcomes measurement enables the researcher to find evidence that examines the same outcome variable (Melnyk & Fineout-Overholt, 2005). This review only includes studies that measured pain numerical rating scales to determine pain intensity mean difference. In contrast, tolerability is measured using every study's occurrence of adverse events and the computed risk ratio of the intervention arm and placebo arm.

Efficacy outcome. The first outcome is the pain intensity difference between the pretest mean pain intensity and post-test mean pain intensity. This outcome measures the efficacy of intervention and placebo in pain management. It is an outcome measure that summarizes treatment response over a clinically relevant period. From the seven included studies that have undergone systematic review, only six studies presented to have quantifiable recorded and available data useful for efficacy determination. The study of Ameronge et al. (2017) did use a numerical rating scale to measure pain for its baseline data. However, the post-test data was not provided, no statistical treatment data was presented and hence

excluded from the list of reviews for efficacy outcomes. The included studies and details on mean pain differences are presented in Table 6 below. The table showed pretest and post-test mean pain intensity for both the intervention arm and placebo arm, absolute mean difference and computed SD, sample sizes for both treatment arms, and CMA software computed standardized mean differences.

Table 6
Mean Pain Difference

	Cannabinoids				Placebo				
Study	**Pretest Mean**	**Post test Mean**	**Mean Difference (SD)**	**Sample Size**	**Pretest Mean**	**Post test Mean**	**Mean Difference (SD)**	**Sample Size**	**SMD (CMA generated)**
1.Schimrigka et al. (2017)	6.4	1.92	-4.48 (2.01)	124	6.74	4.93	-1.81 (1.94)	116	-1.046
2.Fallon et al. (2017)	3.2	3.7	0.5 (1.3)	103	3.1	3.6	0.5 (1.6)	103	0.000
3.Lichtman et al. (2018)	5.6	4.8	-0.8 (1.4)	199	5.6	5	-0.6 (1.5)	198	-0.107
4.Meuth et al. (2020)	5.86	2.37	-3.49 (2.47)	53	5.84	3.81	-2.03 (2.07)	53	-0.496
5.Bebee et al (2021)	7.1	6.2	-0.9 (-1.8)	50	7.4	5.8	-1.6 (-1.4)	50	-0.336
6. Eibach et al. (2021)	3.62	3.29	-0.33 (0.57)	16	5.23	3.25	-1.98 (2.03)	16	-0.857

(-) Mean Difference indicates a decrease in Pain Intensity

Five studies presented above have negative mean differences in both for Cannabinoids and Placebo control indicate a decrease in Pain intensity as measured using the Pain numerical scale instrument. The study of Fallon et al. (2017) opposes the majority of the results. Instead of decreasing pain intensity, it

manifested an increase in pain intensity. Accordingly, the placebo control for this study manifested an increase in pain intensity.

Determining a clinically meaningful outcome requires information about the degree of change over time that is clinically important. The best cut-off point for PID percent was 33 percent and for absolute pain intensity difference of two. These data-derived cut-off points for the changes in several pain scales reflect clinical importance. Using consistent clinically significant cut-off points as the primary outcome in future pain therapy clinical trials will enhance their validity, comparability, and clinical applicability (Farrar et al., 2000). It is consistent with the study of Wang et al. (2019). They suggested that a decrease in pain intensity of ≥ 2 points between the initial and subsequent NRS measurements predicts good pain relief.

Studies one, three, four, and five have been estimated to have at least and greater than two points decrease in the pain intensity—an indication of efficacy in pain management. Evaluating the absolute difference in pain intensity and the percentage difference in pain intensity could facilitate an understanding of pain reduction among cancer patients during repeated hospitalizations. As summarized by a change in mean values over time, differences between groups can be challenging to apply to clinical care. Baseline scores vary widely, and group means differences could reflect significant changes in a few patients, small changes in many patients, or any combination of these outcomes. Determining the proportion of patients with a clinically significant improvement in their pain would provide a more interpretable result with direct clinical implications.

Tolerability Outcomes. The second outcome reviewed in this study was the recorded incidence of adverse events in both treatment arms. According to National Cancer Institute, Adverse events are unexpected medical problems that happen during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe and may be caused by something other than the drug or therapy. In epidemiology, the incidence in health, such as adverse events, is reported as risk. The risk of experiencing adverse events in both treatment arms is compared and reported as a risk ratio.

Of the seven included studies, the study of Meuth et al. (2020) using Nabiximols was excluded from the list on tolerability outcomes because of missing data on the occurrences of declared adverse events experienced by the patients. Another set of six studies qualifies for tolerability assessment. These studies are presented in the table 7 below. The table displays also the incidence of adverse events (a) and population (b) in the intervention arm, the incidence of adverse events (b) and population (d) in the placebo arm, the computed risks for both intervention arm (A) and Placebo arm (B).

Table 7
Calculated Risk of Adverse Events of the Included Studies

Study.	Intervention AE (*a*)	Population (*b*)	Placebo AE (*c*)	Population (*d*)	Intervention Risk (*A= a/b*)	Placebo Risk (*B= c/d*)
1. Schimrigka et al. (2017)	109	124	85	116	0.88	0.73
2.Ameronge et al. (2017)	10	12	7	12	0.83	0.58
3.Fallon et al. (2017)	74	104	64	103	0.72	0.62
4.Lichtman et al (2018)	144	199	130	198	0.72	0.66
5.Bebee et al. (2021)	35	50	42	50	0.70	0.84
6. Eibach et al. (2021)	11	34	27	34	0.32	0.80

In the included studies, there is a record of 383 adverse events from cannabinoids and 355 adverse events from placebo. A total of 738 adverse events. Fifty-two percent of the recorded adverse events are from the cannabinoids, and placebo has an almost equally relevant incidence of forty-eight percent. Only the occurrences of adverse events are included and are substantial in this review. Dizziness, vertigo, fatigue, and somnolence, were generally experienced by most participants in the six studies, except the study of Meuth et al. (2009) which did not contain any reported adverse events.

Risk. In the Cannabinoids group, studies one to five recorded a relatively equal risk of more than 0.70 to 0.88. This can be understood that 70 up to 88 patients out of 100 will risk experiencing adverse events under this treatment arm.

Consequently, study six has a risk value of 0.32, the lowest recorded risk across the two arms of treatment. The observed adverse events are somewhat explained by the chemical nature and pharmacology of the cannabinoids. Their capacity to cross the blood-brain barrier produces adverse events in this central nervous system.

On the contrary, the six studies have at least 0.5 up to 0.84 risk value for the placebo control. About 50 to 84 patients out of 100 will risk experiencing adverse events even taking only a placebo control. According to Lavan and Gallager (2016), adverse drug reactions (ADRs) are common in older adults, with falls, orthostatic hypotension, delirium, renal failure, and gastrointestinal and intracranial bleeding being amongst the most common clinical manifestations. ADR risk increases with age-related changes in pharmacokinetics and pharmacodynamics, increasing the burden of comorbidity, polypharmacy, inappropriate prescribing, and suboptimal monitoring of drugs.

New medications such as Cannabinoids should be prescribed cautiously with clear therapeutic goals and recognizing the impact a drug can have on multiple organ systems. Prescribers should regularly review medication efficacy and be vigilant for ADRs and their contributory risk factors. Deprescribing should occur individually when drugs are no longer efficacious or beneficial or when safer alternatives exist. Inappropriate prescribing and unnecessary polypharmacy should be minimized.

Thus, it is logical to say that the adverse events recorded cannot be attributed solely to the intervention; other factors must be considered, especially

with the results recorded in the placebo control. Comorbidities, blinding effects, environmental factors, and stress can produce the recorded untoward events experienced by the patients during the clinical trial.

The Table 8 below displays the calculated risk ratio of the intervention arm over the placebo control. Note that the treatment arm of interest is the Cannabinoid (intervention), he data of included studies is presented in column A while placebo's data is listed under column B. The incidence of cannabinoid is divided by the incidence in the placebo group generating the risk ration value.

Risk Ratio. The following can be interpreted based on the CDC statement for risk ratio. For study one, studies Dronabinol, patients under this cannabinoid arm were 1.20 times as likely to experience adverse events as those who received a placebo. In a study by Ameronge et al. (2017), which recorded the highest risk ratio, the cannabinoid group is 1.43 times more likely to experience adverse events than the placebo. The study of Fallon et al. (2017) and Licthman (2018), which uses studies of the same Cannabinoid, Nabiximols (Sativex), revealed a risk ratio of 1.16 and 1.10, respectively. Patients receiving Nabiximols, in this case, are 1.16 and 1.10 more likely to experience adverse events than placebo. Bebee et al. (2021) studied the phytocannabinoid Cannabinol; it revealed a risk ratio of 0.83.

Table 8
Calculated Risk Ratio of Adverse Events of the Included Studies

Study	Cannabinoids Risk (A)	Placebo Risk (B)	Risk Ratio (*A/B*)
1. Schimrigka et al. (2017)	0.88	0.73	1.20
2.Ameronge et al. (2017)	0.83	0.58	1.43
3.Fallon et al. (2017)	0.72	0.62	1.16
4.Lichtman et al (2018)	0.72	0.66	1.10
5.Bebee et al.(2021)	0.70	0.84	0.83
6. Eibach et al. (2021)	0.32	0.80	0.41

More so, according to the CDC, a risk ratio of less than one indicates a decreased risk for the exposed group or the cannabinoid, indicating that perhaps exposure protects against disease occurrence. The previous study using Cannabidivarin (Eibach, 2021), a novel and newly developed cannabinoid, recorded the lowest risk ratio of 0.41. Hence, the Cannabidivarin risk ratio indicates that patients under this treatment arm were only approximately 41 percent to experience compared to the placebo arm. The phase two randomized controlled trial of the efficacy and safety of Cannabidivarin as add-on therapy in participants with inadequately controlled focal seizures revealed that the three most common AEs were diarrhea, nausea, and somnolence. The incidence of severe AEs was

low (3.7% in the CBDV group vs. 1.2% in the placebo group), and CBDV was generally well tolerated.

Meta-Analyses of Outcomes

Systematic and strict integration of the verified results from the included studies was performed. The second part of the review entails quantitative analysis. Therefore, meta-analyses were performed to provide a precise and significant summary estimate. The MD and SMD of pain intensity and the risk ratio of adverse event incidence are pooled for two separate analyses. In addition, meta-analysis provided useful listing and exploring sources of bias, aided in quantifying between-study heterogeneity, and proposed some potential explanations for dissecting genuine heterogeneity from bias. More importantly, the effect size is vital for analysis in the meta-analysis. In this review, interventions may vary in specific characteristics, the sample used in each study might be slightly different, or its methods.

The meta-analysis result is based on the random effect model; the generated forest plot presents the overall SMD and risk ratio under the random-effects model. Each study is shown with its effect size and the corresponding 95 percent confidence interval. The random-effects model assumes that the actual effect varies (and is usually distributed). In the random-effects-model, the assumption that the population effect size is normally distributed must be accounted for (Schwarzer et al., 2015). The random-effects model works under the so-called assumption of exchangeability. It has been recommended to use this model for clinical and health sciences research (Cuijpers, 2016). The random-

effects-model pays more attention to small studies when pooling the overall effect in a meta-analysis (Schwarzer et al., 2015). Thus, the random-effects-pooling model is utilized in the meta-analyses results presented below.

Meta-analysis on Efficacy Outcomes

The first meta-analysis performed in this research is using efficacy outcomes presented above. The standardized mean differences of the six qualified studies are analyzed using the CMA software. Results and interpretation are presented below.

Pooled Effect Measures using SMD for Cannabinoids vs Placebo Efficacy for Pain Management

Figure 5 shows the forest plot for the standardized mean differences (SMDs) in the measured outcomes between the Cannabinoids and Placebo groups. The six studies assess the effectiveness of the two groups in pain management.

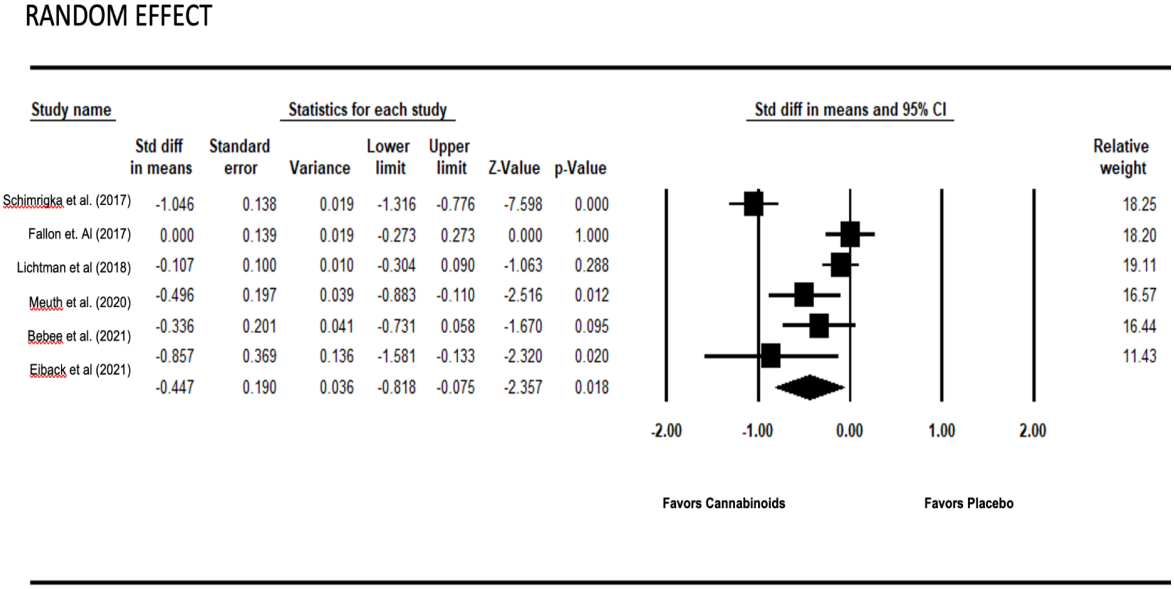


Figure 5. Forest Plot of Efficacy Outcomes

Effect Size and the Null Effect Vertical Line. In this figure, the x-axis indicates the effect size being compared among the selected studies, specifically SMD, in this systematic review since the outcomes are expressed as continuous variables and are expressed using the Pain Numerical Rating Scale. Each SMD value was computed based on the mean difference between the cannabinoids and placebo groups divided by their "pooled" standard deviation. The intervention is considered adequate if the experimental group's mean is lesser than the control's. As shown, the x-axis is conveniently set at a range of - 2.0 to + 2.0. The vertical line that coincides with 0.00 is the line of null effect and, as such, indicates no significant difference in the outcomes between the control and experimental groups. The SMDs to the left denotes an effective intervention; the measured outcome for Cannabinoids is greater than that of the placebo drug. Meanwhile, SMDs to the right of the "null effect" line favor the placebo drug. A negative value of SMDs indicates a decrease in pain intensity post-treatment.

SMDs and 95 percent Confidence Intervals of Individual Studies. Figure 5 also reveals the SMDs of the six studies reviewed, as represented by the black boxes, with their corresponding 95 percent confidence intervals, represented by the "whiskers" on both sides of each black box. The individual SMD, the effect size indicated for each study, and the 95 percent confidence interval is also shown. For instance, Schrimrigka et al. (2017) have shown the greatest SMD = -1.046 among the six studies. Its confidence interval at -1.317, -.0776, implying that within this range, one can be 95 percent certain that the actual SMD lies.

Additionally, a closer examination of the figure reveals that five studies are relatively "close" in weight and, as such, are represented by black boxes of almost the exact sizes. Among the six studies, three with confidence intervals cross the vertical line 0.00, indicating that this study fails to establish the significance of the difference. The rest of the individual studies have significant SMDs as indicated by their p-values and as validated by their "whiskers" not crossing the vertical line of "null effect." Amongst the six studies, three have a p-value less than 0.05, which is very important in analyzing the results. This result shows a significant difference in the mean pain intensity reduction of the cannabinoids over the placebo control. The other three studies have a mean pain intensity difference that favors cannabinoids, yet the p-value implies no significant difference when statistically compared with placebo control.

Overall SMD. As shown by the black diamond in Figure 5, the overall SMD = -0.447 with p-value = 0.018. This result indicates that the outcome for the Cannabinoids group is favorable and higher than the placebo group, implying that Cannabinoids are more effective in pain management compared to the placebo. The overall mean p-value implies a significant difference in the efficacy of cannabinoids when statistically compared with placebo control. Correspondingly, the 95 percent confidence interval is -0.818, -0.075, which indicates 95 percent certainty that the true SMD lies within this range of values.

Heterogeneity. The extent to which effect sizes vary within a meta-analysis is called heterogeneity. It is essential to assess heterogeneity in meta-analyses, as between-studies differences could cause high heterogeneity. Such information

could be precious for research because this might allow us to find interventions or populations for which effects are lower or higher (Borenstein et al., 2011).

Table 9
Heterogeneity of Included Studies for Efficacy Outcomes

Heterogeneity				Tau-squared			
Q-value	df(Q)	p-value	i-squared	Tau squared	Standard error	Variance	Tau
40.169	5	0.000	87.553	0.178	0.146	0.021	0.422

The Q-test provides Cochran'sCochran's Q value = 40. 169 with a p-value = 0.000 that the individual studies SMDs do not statistically evaluate the same effect size concerning the overall SMD. It indicates that there are indeed substantial differences underlying the results of the studies. Although the power of Q, in this case, is not high due to the limited number of included studies, there is a hint of heterogeneity in these studies. Reject the hypothesis that there is no heterogeneity.

The I*2* statistic describes the percentage of variation across studies due to heterogeneity rather than chance. As revealed in the same table, this collection of studies has established an I*2* = 87.553 percent. This value denotes substantial heterogeneity based on Cochrane'sCochrane's specifications, implying the variability across the studies that may be used as the basis for further subgroup analysis. The next test is the $T2$ test, which measures the dispersion of true effect sizes between studies in terms of the scale of the effect size. It is also an estimate of the variance of the true effect sizes. $T2$ also represents the absolute value of

the true variance (heterogeneity). In this study, the software-generated that the true effect sizes between the six studies are dispersed at 0.442 in terms of the scale of the effect size.

Publication Bias. It is essential to examine the results of each meta-analysis for evidence of publication bias. An estimation of the likely size of the publication bias in the review and an approach to dealing with the bias is inherent to the conduct of many meta-analyses. A funnel plot provides a graphical evaluation of the potential for bias. A funnel plot is a scatterplot of treatment effect against a measure of study size. If publication bias is not present, the plot is expected to have a symmetric inverted funnel shape, as shown in Figure 6.

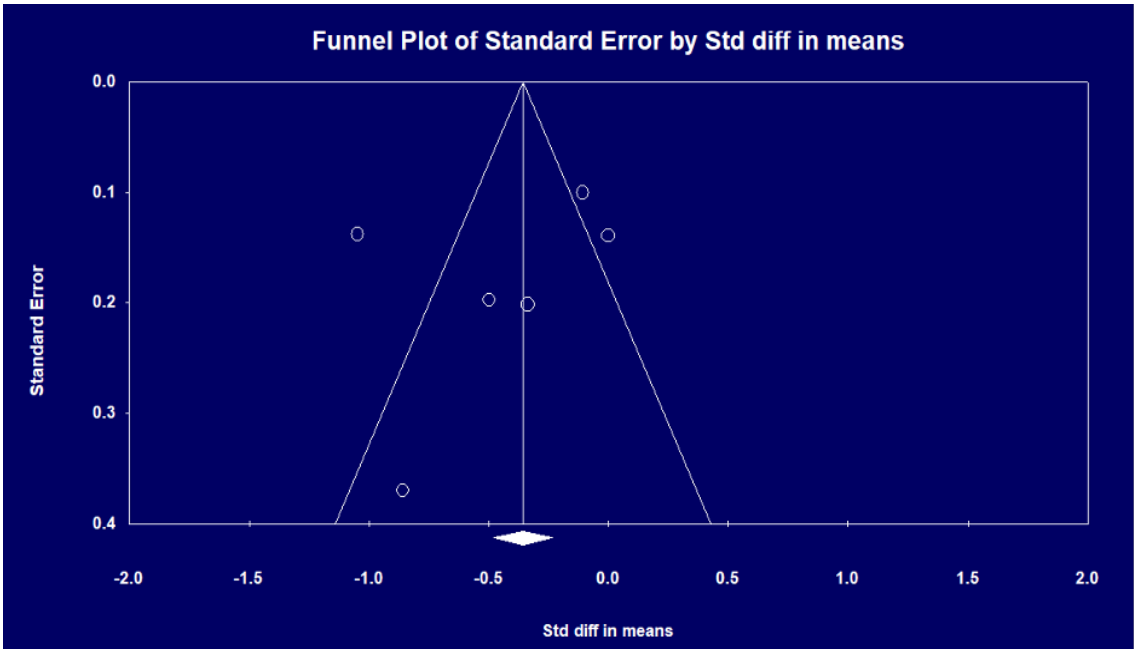


Figure 6. Funnel Plot of Included Studies for Efficacy Outcomes

Figure 6 shows the funnel plot to describe the publication bias with respect to the six studies selected for this meta-analysis. A publication bias pertains to the failure to include all relevant studies because they were not published and were

therefore not accessible. Publication bias results in asymmetry of the funnel plot. As shown in figure 6, there is evidently a publication bias since the dots representing the studies selected did not establish symmetry with respect to the vertical line, which represented the total overall estimate or the standard mean difference revealed by the six studies. Asymmetry of funnel plots is not solely attributable to publication bias, but may also result from clinical and methodological variations (Haidich, 2010). To further address the publication bias, Classic Fail-safe N was performed.

Classic Fail-safe N of included studies. These values in Table 10 revealed vital information to measure the publication bias of this meta-analysis done in 6 included studies.

Table 10
Classic Fail-safe N of included studies for Efficacy Outcomes

	Classic fail-safe N
Z-value for observed studies	-6.192076
P-value for observed studies	0.00000
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95995
Number of observed Studies	6.0000
Number of missing studies that would bring p-value to > alpha	54.0000

Table 10 presents the generated data from the CMA software. These values revealed vital information to measure the publication bias of this meta-analysis

done in the six studies selected. Suppose a meta-analysis reports a significant p-value based on studies. Researchers are concerned that studies with smaller effects are missing. If all the missing studies were retrieved and included in the analysis, the p-value for the summary effect would no longer be significant. Rosenthal (1979) suggested to compute the missing studies we would need to retrieve and incorporate into the analysis before the p-value became nonsignificant.

Table 10 values reveal vital information to measure the publication bias of this meta-analysis done in the six studies selected. It shows that 54 studies are missing that would bring the p-value to a number greater than 0.05. It implies that at least 54 studies with nonsignificant effects are needed to make the overall effect or SMD value nonsignificant. The failsafe number estimates the number of 261 additional studies to turn the effect size from the included and additional studies combined insignificant, that the 'new' combined effect size is essentially zero.

The four cannabinoids employed as interventional treatment in the six clinical trials reviewed clinical efficacy in pain management. Consistently, it was revealed in the statistical analysis done that there is a significant difference in the mean pain intensity difference between the two treatment arms. The outcomes of the analysis favor the Cannabinoids as more effective in pain management than the placebo control. The six studies presented variability in their features, which was revealed in the heterogeneity test. Hence it can be a limitation of the study. However, the random effect model was used in the analysis to neutralize this heterogeneity.

Meta-Analysis on Tolerability Outcomes

This meta-analysis was performed using the risk ratio to assess the tolerability outcomes. The second set of six qualified studies are analyzed using the CMA software. Results and interpretation are presented below.

Pooled effect measures using Risk ratio on Adverse Events Incidence of Cannabinoids vs Placebo for Tolerability Outcomes

The effect measures or the statistical constructs utilized to compare tolerability outcome data between the two groups is called risk ratio. For ratio effect measures, a value of one represents no difference between the groups as shown in Figure 7.

The forest plot for the risk ratio in the measured outcomes between the Cannabinoids and Placebo groups. The six studies assess the tolerability of the two groups in pain management. The values of ratio measures of intervention effect usually undergo log transformations before being analyzed, and they may occasionally be referred to in terms of their log-transformed values. Ratio summary statistics all have the standard features: the lowest value they can take is zero, the value one corresponds to no intervention effect, and the highest value they can take is infinity. This number scale is not symmetric (Higgins, 2022).

Effect size and the null effect vertical line. The figure above demonstrates the effect size being compared among the selected studies, particularly the risk ratio. Tolerability outcomes are expressed as dichotomous variables using risk and risk ratio. Each risk ratio was computed based on the

incidence of adverse events published in every study between the cannabinoids and placebo groups.

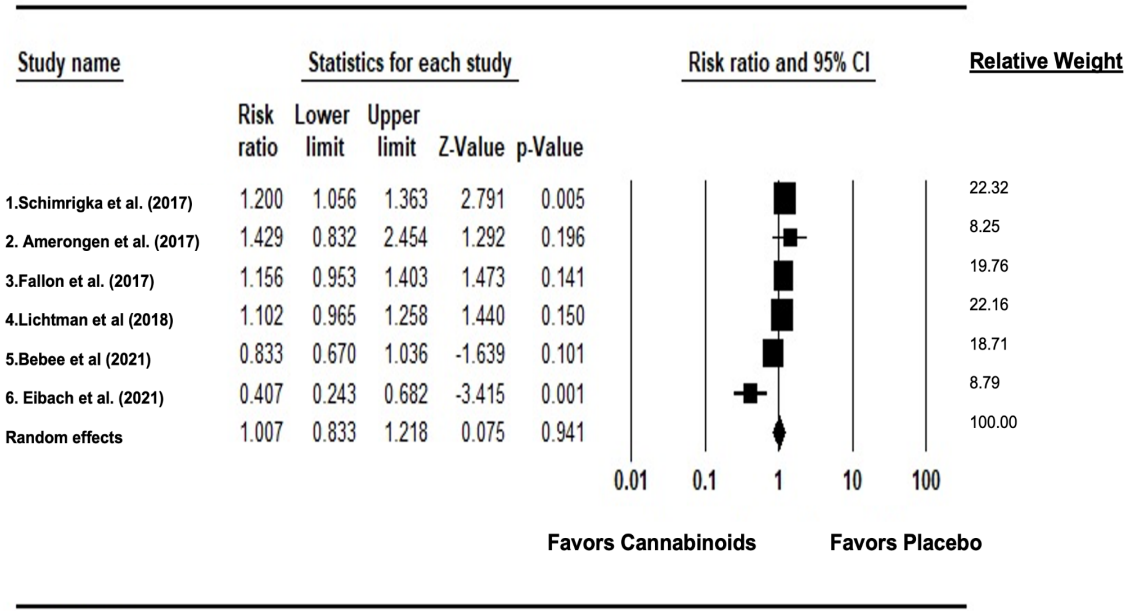


Figure 7. Pooled Effects Measures on Adverse Events of Included Studies

The intervention is considered tolerable if the risk is more negligible compared to a placebo. Thus, a risk ratio of less than one favors the cannabinoids, while a risk ratio of more than one favors the placebo control. The vertical line that coincides with one is the null effect line and, as such, indicates no significant difference in the outcomes between the cannabinoids and placebo groups (Higgins, 2022).

Risk Ratios and 95 percent Confidence Intervals of Individual Studies. Figure 7 also reveals the risk ratios of the six studies reviewed, as represented by the black boxes, with their corresponding 95 percent confidence intervals, represented by the "whiskers" on both sides of each black box. The individual RR, as the effect size, is indicated for each study, and the 95 percent confidence

interval is also shown. For instance, study Amerongen et al. (2017) have shown the highest RR = 1.429 among the six studies. Its confidence interval at 0.832, 2.454, implying that within this range, one can be 95 percent certain that the true risk lies. Further, a closer examination of the figure reveals that studies 1 and 4 are relatively "bigger" studies and, as such, are represented by black boxes of larger sizes. Hence, a more significant number of participants establishes a "narrower" confidence interval (Higgins, 2022). Among the six studies, five whose confidence interval crosses the vertical line at 1.0, indicating that this study fails to establish the significance of the difference, indicated by the p-values of more than 0.05 in the figure above. Only one study, the one on Cannabidivarin, has significant RR as indicated by its p-values (0.001) and as validated by its "whiskers" not crossing the vertical line of "null effect." This result implies that the tolerability shown in this study is significantly different from the placebo. Cannabidivarin is a new drug, and this finding can be an opportunity to investigate more about it since it is significantly different from the other cannabinoids in terms of tolerability.

Overall SMD. As shown by the black diamond in Figure 7, the overall RR = 1.007 with p-value = 0.941. The confidence interval crosses the vertical line at 1.0, indicating that this study fails to establish significance of the difference. This result indicates that the Cannabinoid treatment arm and Placebo control arm tolerability is comparable statistically. Correspondingly, the 95 percent confidence interval is 0.833, 1.218, which indicates it is of 95 percent certainty that the true risk lies within this range of values. This result implies that even there are more incidence of adverse events in the cannabinoid arm over the placebo, yet it did not establish

statistical significant difference. Adverse events are part of drug therapy. Placebo, however, is an contains no active ingredients. It is not supposed to cause the patient anything. This statistical finding is an advantageous and favors cannabinoids. Hence, adverse events occurs inevitably.

Heterogeneity of Included Studies for Tolerability Outcomes. The Q-test generates a Q value =23.335 with a p-value = 0.00, indicating that the individual studies' RRs do not statistically evaluate the same effect size concerning the overall RR. It indicates that there are indeed genuine differences underlying the results of the studies. Although the power of Q, in this case, is not high due to the limited number of included studies, there is a hint of heterogeneity in these studies.

Table 11
Heterogeneity of Included Studies for Tolerability Outcomes

Heterogeneity				Tau-squared			
Q-value	df(Q)	p-value	i-squared	Tau squared	Standard error	Variance	Tau
23.335	5	0.000	78.573	0.038	0.036	0.001	0.195

Reject the hypothesis that there is no heterogeneity (Higgins, 2022). The I2 statistic describes the percentage of variation across studies due to heterogeneity rather than chance. As revealed in the same table, this collection of studies has established an I2 = 78.573 percent. This value denotes substantial heterogeneity, implying the variability across the studies that may be used as the basis for further subgroup analysis (Higgins, 2022). In this study, the CMA

software-generated that the true effect sizes between the six studies are dispersed at 0.195 in terms of the scale of the effect size.

Publication Bias. If publication bias is not present, the plot is expected to have a symmetric inverted funnel shape, as shown in Figure 8.

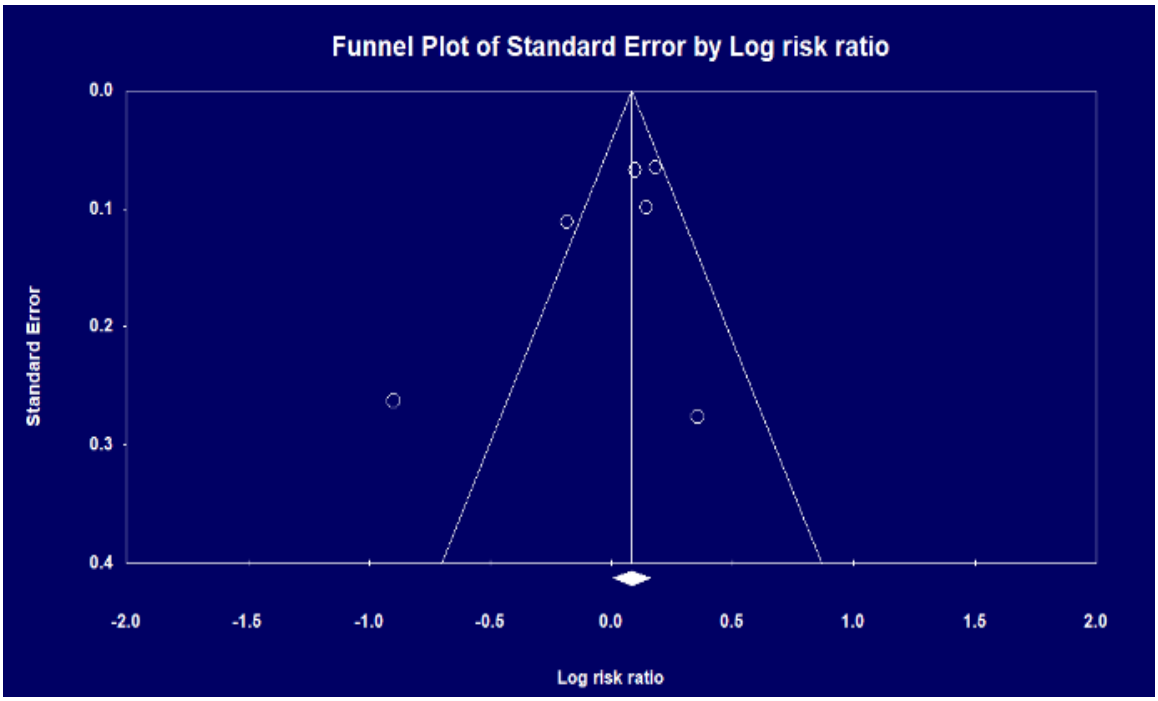


Figure 8. Funnel Plot of Included Studies

Figure 8 shows the funnel plot to describe the publication bias concerning the six studies selected for this meta-analysis. As shown, there is a publication bias since the dots representing the studies selected did not establish symmetry concerning the vertical line, representing the total overall estimate revealed by the six studies..

Classic Fail-safe N. Table 12 presents the generated values that revealed vital information to measure the publication bias of this second meta-analysis done

in the different sets of 6 studies for tolerability outcomes. Suppose a meta-analysis reports a significant p-value based on studies. It shows that no more studies are needed to bring the p-value to a number greater than 0.05. It implies that the six studies analyzed are sufficient to make the overall effect or SMD value non-significant.

Table 12
Classic Fail-safe N of included studies for Tolerability Outcomes

	Classic Fail-safe N
Z-value for observed studies	0.68622
P-value for observed studies	0.49257
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed Studies	6.0000
Number of missing studies that would bring p-value to > alpha	0.0000

Hence, tolerability assessment on the four cannabinoids employed as interventional treatment in the six clinical trials reviewed versus the placebo control revealed comparable results. Clinically, the patients on both arms experienced adverse events while receiving treatments. It was revealed in the forest plot that there is no significant difference in the tolerability of cannabinoids and placebo control. Both treatment arms cause the patients adverse events.

This result can be favorable for cannabinoids since it is apprehended due to adverse events. It can be seen in the results that a placebo has provided no

clinical and statistical difference from the Cannabinoids. It can be implied that adverse events occur unexpectedly as part of the therapy. Also, it can be brought by preconceived The six studies presented variability in their features, which was revealed in the heterogeneity test. Hence it can be a limitation of the study. However, no additional studies are needed to change the comparable outcomes of cannabinoids and placebo in terms of tolerability.

Chapter 4

CONCLUSION AND RECOMMENDATIONS

This chapter presents the conclusions drawn from the findings and the corresponding recommendations for this systematic review and meta-analysis.

Conclusions

The seven clinical trials represented adult patients who have experienced either chronic or acute pain due to existing conditions and seek and deserve the best pain relief and tolerable therapy possible. Cannabinoids, either natural or synthetically derived, have the potential to manage pain and aid and protect existing analgesics. After reviewing the seven included studies, there are four kinds of cannabinoid interventions identified. This includes Nabiximols, Dronabinol, Cannabidiol, and Cannabidivarin provided pain relief to the patients even if there are adverse events.

Based on the clinical data gathered from each study and the statistical results, it can be inferred that Cannabinoids provide pain relief and are significantly different compared to placebo. Hence, cannabinoids are more effective in pain management than placebo. The efficacy manifested in this review is a good start to engaging and increasing education on the promising medical benefits of cannabinoids. The patient's tolerability of the therapy is comparable between cannabinoids and placebo, as revealed in the overall risk ratio's p-value. The adverse events recorded in the Cannabinoid treatment arm are equal to placebo control. Preconceived thoughts regarding the illicit use of the plant might contribute to the adverse effects felt by the patients, aside from the comorbidities and

discomforts from the environment. The results of this review are, therefore, helpful for clinical care. Medicines anciently began from plants, and technology refined them to address worldwide demands. Thus, through responsible research and advanced technology, it is imperative to make way and maximize the gift of nature in the form of Cannabinoids.

Recommendations

This study has significant implications in clinical care. Based on the conclusion, the following are recommended:

Based on the results of Cannabinoids' efficacy outcomes, the clinical data is limited to the Caucasian race only. It is recommended that the pharmaceutical companies expand the scope of the existing clinical trials by including other races to have more generalizable data on the potential of cannabinoids in pain management. Further detail on the expansion is to compare cannabinoids against the standard pain management such as non-opioids, opioids, and combinational approaches to see the bigger picture and benefits that the cannabinoids can provide to patients and the community.

The tolerability outcomes of cannabinoids, as revealed in the clinical and statistical results, were comparable with placebo. However, it cannot be denied that these occurrences may hinder patients from participating further in clinical trials. Hence, it is recommended that medical chemists and the pharmaceutical industry explore the existing cannabinoids available in the market to diminish this incidence of adverse events. In order to do so, the routes of administration, dosage, and frequency can be manipulated to control the occurrence of adverse

events. In addition, it is recommended to increase the duration of therapy and categorize recorded adverse events according to organ system before, during, and after cannabinoid trial for more detailed adverse event reporting.

The general results of this study on efficacy and tolerability give light to the public's apprehensions about cannabinoids. The benefits presented in the included studies outweigh the harm expected from cannabinoids. Furthermore, future researchers may utilize different research designs; such an observation approach using a cohort type of research can provide more robust clinical data and substantial statistical implications to have a complete appraisal and concretize evidence-based medicine pharmacotherapy. Another recommendation can be given to the government and lawmakers in light of the efficacy and tolerability manifested by cannabinoids. It is recommended that lawmakers review the available clinical evidence and open conversation on possible amendments to the restrictions imposed on using cannabinoids as medicine here in our country.

REFERENCES

Abuhasira, R., Schleider, L., Mechoulam, R., & Novack, V. (2018). Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. *European Journal on Internal Medicine*. Retrieved from http://www.ejinme.com/article/S0953-6205(18)30019-0/abstract.

Almog, S., Aharon-Peretz, J., Vulfsons, S., Ogintz, M., Abalia, H., Lupo, T., . . . Eisenberg, E. (2020, September 1516). The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial. *European Journal on Pain, 24*(8), 1505.

Amar, M. (n.d.). Cannabinoids in medicine: A review of their therapeutic potential. *Journal on Ethnopharmacology, 105*, 1-25.

Andrade, C. (2020, September). Mean difference, Standardized Mean Difference (SMD), and Their Use in Meta-Analysis. *The Journal of Clinical Psychiatry*.

Andreae, M., Carter, G., Shaparin, N., Suslov, K., Ellis, R., Ware, M., . . . Sacks, H. (2015). Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *Journal for Pain, 16*(12), 1221-1232.

Aoyama, T., Ishida, Y., & Kaneko, M. (2017, December). Pharmacokinetics and Pharmacodynamics of Meloxicam in East Asian Populations: The Role of Ethnicity on Drug Response. *CPT: Pharmacometrics and Systems Pharmacology, 6*(12). Retrieved from https://doi.org/10.1002/psp4.12259

Argoff, C. (2017, May 10). *Types of Pain.* Retrieved from Pharmaceutical Pain Management: https://www.practicalpainmanagement.com/pain/distinguishing-neuropathic-non-neuropathic-mixed-pain

Attal, N., Lanteri-Minet, M., Laurent, B., Fermanian, J., & Bouhassira, D. (2011, December). The specific disease burden of neuropathic pain: results of a French nationwide survey. *Pain, 152*(12), 2836-2843.

Boland, E., Bennett, M., Allgar, V., & Boland, J. (2020, March). Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. *BMJ Support and Palliative Care, 10*(1), 14-24.

Baron, E. P. (2015, May). Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been …. *Headache: The Journal of Head and Face Pain, 55*(6), 885-916.

Bebee, B., Taylor, D., Bourke, E., Pollack, K., Foster, L., Ching, M., & Wong, A. (2021, May). The CANBACK trial: a randomised, controlled clinical trial of oral cannabidiol for people presenting to the emergency department with acute low back pain. *The Medical Journal of Australia, 214*(8), 370-375.

Bridgeman, M. B., & Abazia, D. T. (2017). Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. *Pharmacy and Therapeutics, 32*(3), 180-188.

Bordons, M., Costas, R., & Aparicio, J. (2013). Heterogeneity of collaboration and its relationship with research impact in a biomedical field. *Scientometrics, 96*, 443-466.

Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2011). Introduction to Meta-Analysis. *John Wiley & sons*.

Capano, A., Weaver, R., & Burkman, E. (2020, January). Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. *Postgraduate Medicine, 132*(1), 56-61. Retrieved November 11, 2021, from https://pubmed.ncbi.nlm.nih.gov/31711352/

Carter, G., Duong, V., Ho, S., & Ngo, K. (2014, May). Side effects of commonly prescribed analgesic medications. *Physical Medicine and Rehabilitation Clinics of North America, 25*(2), 457-470.

Colloca, L., Ludman, T., Bouhassira, D., Baron, R., Dickenson, A., Yarnitsky, D., . . . Finnerup, N. (2017, March). Neuropathic pain. *Nature reviews. Disease primers, 3*. Retrieved November 11, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5371025/

Dallel, R. (2020, March 14). Advances in the understanding and treatment of pain and headache. *Journal of Neural Transmission, 127*, 389-392.D'hooghe, M., Willekens, B., & Delvaux, D. (2021). Sativex® (nabiximols) cannabinoid oromucosal spray in patients with resistant multiple sclerosis spasticity: the Belgian experience. *BMC Neurology, 21*(227).

Dworkina, R., Turkb, D., Farrarc, J., & Haythornthwaited, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *International Association for the Study of Pain, 113*, 9-19.

Dydyk, A. M., & Conermann, T. (2021, November). Chronic Pain. StatPearls Publishing.

Egger, M., Smith, G., & Sterne, J. (2001). Uses and abuses of meta-analysis. *Clinical Medicine, 1*(16).

Eibach, L., Scheffel, S., & Cardebring, M. (2020). Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial. *Clinical Pharmacology Therapeutics*.

Farrar, F., Portenoy, R., Berlin, B., & Kinman, J. (2000, December). Defining the clinically important difference in pain outcome measures. *Pain, 88*(3), 287-294.

Finnerup, N. (2015). Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurology, 14*, 162–173.

Flachenecker, P., Henze, T., & Zettl, U. (2014). Nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice--results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. *European Neurology, 71*(5), 271-279.

Foster, N., Anema, J., Cherkin, D., Chou, R., Cohen, S., Gross, D., . . . Maher, C. (2018, June). Prevention and treatment of low back pain: evidence, challenges, and promising directions. *Lancet Low Back Pain Series Working Group, 391*.

Girach, A., Julian, T. H., Varrassi, G., Paladini, A., Vadalouka, A., & Zis, P. (2019). Quality of life in painful peripheral neuropathies: a systematic review. *Pain Research and Management*, *2019*.

Greimel, E. R., Kuljanic Vlasic, K., Waldenstrom, A. C., Duric, V. M., Jensen, P. T., Singer, S., ... & European Organization for Research and Treatment of Cancer Quality-of-Life Group. (2006). The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer*, *107*(8), 1812-1822.

González-Cano, R., Ruiz-Cantero, M. C., Santos-Caballero, M., Gómez-Navas, C., Tejada, M. Á., & Nieto, F. R. (2021). Tetrodotoxin, a potential drug for neuropathic and cancer pain relief?. *Toxins*, *13*(7), 483.

Gopalakrishnan, S., & Ganeshkumar, P. (2013). Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. *Journal of Family Medicine and Primary Care, 2*(1).

Harrer, M., Ebert, D., Cuijpers, P., & Furukawa, T. (2021). *Doing Meta-Analysis with R: A Hands-On Guide.* Chapman and Hall/CRC.

Hazekamp, A., & Grotenhermen, F. (2010). Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids, 5*, 1-21.

Higgins, J. (2022). *Cochrane Handbook for Systematic Reviews of Interventions.* (T. Li, & J. Deeks, Eds.) Cochrane.

Hoffberg, H. (2015, June 25). *Pharmaceutical Treatment of the Cancer Pain Patient.* Retrieved November 11, 2021, from Practical Pain Management:

https://www.practicalpainmanagement.com/pain/cancer/pharmaceutical-treatment-cancer-pain-patient

Iskedjian, M., Bereza, B., Gordon, A., Pickow, C., & Einarson, T. (2007). Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Current Medical Research and Opinion, 23*(1), 17-24.

Jadad, A., Andrew, M., Dawn, C., Crispin, J., & Reynolds, J. (1996). Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Controlled Clinical Trials, 17*, 1-12. Retrieved from https://pubmed.ncbi.nlm.nih.gov/8721797/

Johnson, J., Burnell-Nugent, M., Lossignol, D., Doina Ganae-Motan, E., Potts, R., & Fallon, M. (2010, February). Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *Journal of Pain and Symptom Management, 39*(2), 167-169. Retrieved November 11, 2021, from https://pubmed.ncbi.nlm.nih.gov/19896326/

Jones, K. (2018, August). Strategies for globalizing research in the educational sciences.

Kjaergard, L., Villumsen, J., & Gluud, C. (2001). Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine, 135*(11), 982-989.

Köstenberger, M., Nahler, G., Jones, T., Likar, R., & Neuwersch, S. (2021, Aug). The Role of Cannabis, Cannabidiol and Other Cannabinoids in Chronic Pain. The Perspective of Physicians. *Journal of Neuroimmune Pharmacology*.

Martín-Sánchez, Furukawa, & Taylor. (2009). Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med, 10*.

Mikolajewicz, N., & Komarova, S. V. (2019). Meta-Analytic Methodology for Basic Research: A Practical Guide. *Frontiers Physiology*.

Meng, H., Johnston, B., Englesakis, M., & Moulin, D. (2017). Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis. *Anesthesia and Analgesia, 125*(5), 1638-1652.

Möller, H.-J. (2011, June). Effectiveness studies: advantages and disadvantages. *Dialogues in Clinical Neuroscience, 13*(2), 199-207.

Mori, K., & Toyoshima, S. (2009). Recent approaches by the PMDA to promoting new drug development: change in the status of the PMDA in relation to new drug development over the last five years. *Drug Information Journal, 43*, 47-55.

Mücke, M., Carter, C., Cuhls, H., Prüß, M., Radbruch, L., & Häuser, W. (2016). Cannabinoids in palliative care: Systematic review and meta-analysis of efficacy, tolerability and safety. *SCHERMZ, 30*, 25-36.

National Center for Biotechnology Information. (2022). Retrieved May 28, 2022, from National Library for Medicine: https://pubchem.ncbi.nlm.nih.gov/compound/Cannabidivarin.

Okpeku, J., Costales, Alipour-Haris, Morris, Hincapie-Castillo, Stetten, . . . Adkins. (2021, February). A Mapping Literature Review of Medical Cannabis Clinical Outcomes and Quality of Evidence in Approved Conditions in the USA from 2016 to 2019. *Medical Cannabis Cannabinoid, 4*(1), 21-42. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34676348/

Pergolizzi, J., Raffa, R., & Nalamachu, S. (2013). The basics of breakthrough pain: transmucosal fentanyl. *Practical Pain Management, 12*(3), 46-52.

Pound, P., & Campbell, R. (2015). Exploring the feasibility of theory synthesis: A worked example in the field of health related risk-taking. *Social Science and Medicine, 124*.

Saling, J. (2022). What Is the Placebo Effect? *Pain Management*.

Schimrigk, S., Marziniak, M., Neubauer, C., Kugler, E., Werner, G., & Abramov-Sommariva, D. (2017). Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients. *European Neurology, 78*(5-6), 320-329. Retrieved November 2021

Schwarzer, Guido, Hiam Chemaitelly, L. J.-R., & Rücker, G. (2019). Seriously Misleading Results Using Inverse of Freeman-Tukey Double Arcsine Transformation in Meta-Analysis of Single Proportions. *Research Synthesis Methods*, 476-483.

Spahr, N., Hodkinson, D., Jolly, K., Williams, S., Howard, M., & Thacker, M. (2017). Distinguishing between nociceptive and neuropathic components in chronic low back pain using behavioural evaluation and sensory examination.

Musculoskeletal Science & Practice, 27, 40-48. Retrieved November 11, 2021

Tuttle, A., Tohyama, S., Ramsay, T., Kimmelman, J., Schweinhardt, P., Bennett, G., & Mogil, J. (2015, December). Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. *Pain, 156*(12), 2616-2626.

van de Donk, T., Niesters, M., Kowal, M., Olofsen, E., Dahan, A., & van Velzen, M. (2019). An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain, 160*(6), 860-869.

Wang, Chu, Wu, Sung, Ho, & Pan. (2019). Evaluation of the pain intensity differences among hospitalized cancer patients based on a nursing information system. *PLoS ONE*.

Wang, D., & Bakhai, A. (2006). *Clinical Trials: A Practical Guide to Design, Analysis, and Reporting.* Remedica Medical Education and Publishing.

Whiting, Wolff, Deshpande, Di Nisio, Duffy, & Hernandez. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA, 313*, 2456-2473.

Wiffen, Wee, Bell, & Moore. (2017). Opioids for cancer pain—An overview of Cochrane reviews. *Cochrane Database for Systematic Review*.

World Health Organization. (1996). *Cancer Pain Relief: With a Guide to Opioid Availability.* Retrieved November 11, 2021, from World Health Organization: http://whqlibdoc.who.int/publications/9241544821.pdf.

Xu, D. H., Cullen, B. D., Tang, M., & Fiang, Y. (2020). The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. *Current Pharmaceutical Biotechnology, 21*(5), 390-402. Retrieved from https://pubmed.ncbi.nlm.nih.gov/31793418/

Yekirrala, A., Roberson, D., & Bean, B. (2017). Breaking barriers to novel analgesic drug development. *Nature Reviews Drug Discovery*, 545-564.

DiPiro J.T., &. Y. (2020). *Pharmacotherapy: A Pathophysiologic Approach, 11e.* McGraw Hill

E-Books

Cancer pain: Relief is possible. (2021, February 12). Retrieved from Mayo Clinic: https://www.mayoclinic.org/diseases-conditions/cancer/in-depth/cancer-pain/art-20045118

Cannabivarin National Center for Biotechnology Information. (2022). Retrieved May 28, 2022, from National Center for Biotechnology Information: https://pubchem.ncbi.nlm.nih.gov/compound/Cannabidiol.

Efficacy Guidelines. (1998, September). Retrieved May 15, 2022, from ICH Official web site : ICH: https://www.ich.org/

How old research data can we use for the journal publication? (2018, December 29). Retrieved May 27, 2022, from ResearchGate: https://www.researchgate.net/post/How_old_research_data_can_we_use_for_the_journal_publication

RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. (n.d.). Retrieved January 14, 2022, from Cochrane Methods:

https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

Pathophysiology and Treatment of Chronic Non-Neuropathic Pain: Which Role for Non-Invasive Brain Stimulation? (n.d.). Retrieved November 2, 2021, from frontiersin.org: https://www.frontiersin.org/research-topics/6644/pathophysiology-and-treatment-of-chronic-non-neuropathic-pain-which-role-for-non-invasive-brain-stim#:~:text=The%20label%20of%20chronic%20non,'t%20follow%20any%20...

Public summary of opinion on orphan designation. (2018, April). *European Medicines Agency*.

APPENDICES

APPENDIX A

Certificate of Exemption

University of the Immaculate Conception-Research Ethics Committee

Certificate of Exemption

February 14, 2022

Ferlien Mae Brieta
University of the Immaculate Conception
Fr. Selga Street, Davao City

Re: **EFFICACY AND TOLERABILITY OF SELECTED CANNABINOIDS FOR PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS**

Protocol Code: **CCC-GS-03-02-2022**

Subject: **Certificate of Exemption from Review**

Dear **Ms. Brieta**:

This is to acknowledge receipt of your request and the following supporting documents on February 2, 2022.

- **Letter of endorsement for ethics review from UIC Graduate School**
- **Minutes from the technical panel for the proposal defense**
- **Protocol/thesis proposal approved by the technical panel**
- **Protocol information form for exemption (PIFE)**
- **Filled out application forms for UIC-REC full board review**

After a **PRELIMINARY** review on February 12, 2022 of the above documents, the UIC-Research Ethics Committee deemed it appropriate that the above proposal be EXEMPTED FROM REVIEW.

This means that the study may be implemented without undergoing an expedited or full review. Neither will the researcher/investigator be required to submit further documents to the committee as long as there is no amendment nor alteration in the proposal/protocol that will change the nature of the study nor the level of risk involved.

Very truly yours,

Renan P. Limjuco, PhD
Chair, UIC-REC

APPENDIX B

Endorsement for Pre-final Defense

University of the Immaculate Conception-Research Ethics Committee

ENDORSEMENT FOR PRE-FINAL DEFENSE

May 31, 2022

FERLIEN MAE BRIETA
University of the Immaculate Conception
Fr. Selga Street, Davao City

Re: **EFFICACY AND TOLERABILITY OF SELECTED CANNABINOIDS FOR PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS**

Protocol Code: **CCC-GS-03-02-2022**

Subject: **UIC-REC Endorsement for Pre-final Defense**

Dear **MS. BRIETA:**

This is to acknowledge receipt of the following supporting documents on May 31, 2022.

- **Full Manuscript with Abstract**
- **Letter of Request for UIC-REC Endorsement for Pre-final Defense**
- **Filled out Protocol Final Report form for UIC-REC filing**

Upon the verification of the submitted terminal documents, the UIC-REC officially approves and releases the **Endorsement for Pre-final Defense** for your study titled **EFFICACY AND TOLERABILITY OF SELECTED CANNABINOIDS FOR PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS.**

The UIC-REC commends your commitment to assure the technical and ethical merits of your investigation.

Very truly yours,

Renan P. Limjuco, PhD
Chair, UIC-REC

APPENDIX C

Raw Data During Data Gathering Process

Code	Title	Authors	Year	Randomization	Blinded	Clinical Trial	P	I	C	O
CIM0021	Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy	Mark S. Wallace, MD, Thomas D. Marcotte, PhD, Anya Umlauf, MS, Ben Gouaux, BA, J.H. Atkinson, MD	2015	yes	double blinded	Cross over design	Adults, DM	Inhaled Cannabis	Placebo	Pain Severity (VAS), AE
CIM0022	Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial	Dana Turcotte, PhD, Malcolm Doupe, PhD,Mahmoud Torabi, PhD,Andrew Gomori, MD,Karen Ethans, MD,§ Farid Esfahani, MD,Katie Galloway, MSc,and Mike Namaka, PhD	2015	yes	double blinded	Yes	Adults, MS	Nabilone	Placebo	Pain Severity (VAS), AE
CIM0023	A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain	B. Hoggart, S. Ratcliffe, E. Ehler, K. H. Simpson, J. Hovorka, J. Lejcˇko, L. Taylor, H. Lauder, M. Serpell	2015	yes	double blinded	Yes	Adults	THC/CBD Spray	Placebo	Pain Intensity (NRS); Adverse Events

CIM0025	Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability	Marjan de Vries, Dagmar C. M. van Rijckevorsel, Kris C. P. Vissers, Oliver H. G. Wilder-Smith & Harry van Goor1	2015	yes	double blinded	Cross over design	Adults, Opiod and Non Opioid User	Namisol	Diazepam	Pain Severity (VAS), AE
CIM0027	Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial	Z. Malik, L. Bayman, J. Valestin, A. Rizvi-Toner, S. Hashmi, R. Schey1,2	2016	yes	double blinded	Yes	Adults	Dronabinol	Placebo	SF 36 Questionnaire
CIM0028	Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study	Marjan de Vries, Dagmar C.M. van Rijckevorsel, Kris C.P. Vissers, Oliver H.G. Wilder-Smith, Harry van Goor	2016	yes	double blinded	Parallel group trial	Adults	Namisol	Placebo	Pain Severity (VAS), AE
CIM0071	An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease	Barth Wilsey, MD, Thomas D. Marcotte, PhD,, Reena Deutsch, PhD,, Holly Zhao, MD, PhD, A Hannah Prasad, Amy Phan, Research Associate	2016	yes	double blinded	Cross over design		THC		Pain Severity (VAS)

CIM0026	Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients	Sebastian Schimrigka Martin Marziniakb Christine Neubauerc Eva Maria Kuglerc Gudrun Wernerc Dimitri Abramov-Sommarivac	2017	yes	double blinded	Parallel group trial	Adults	Dronabinol	Placebo	Pain Intensity (NRS); Adverse Events
CIM0031	Effects on Spasticity and Neuropathic Pain of an Oral Formulation of Δ9-tetrahydrocannabinol in Patients WithProgressive Multiple Sclerosis	Guido van Amerongen,; Kawita Kanhai,; Anne Catrien Baakman,; Jules Heuberger,; Erica Klaassen,; Tim L. Beumer, Rob L.M. Strijers, MD, Joep Killestein, MD, Joop van Gerven, MD1; Adam Cohen,and Geert Jan Groeneveld, MD,	2017	yes	double blinded	Parallel group trial	Adults	Δ9-tetrahydrocannabinol (ECP002A)	Placebo	Pain Intensity (NRS); Adverse Events
CIM0066	Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies	Marie T Fallon,, Eberhard Albert Lux, Robert McQuade5, Sandro Rossetti, Raymond Sanchez, Wei Sun, Stephen Wright, Aron H Lichtman and Elena Kornyeyeva	2017	yes	double blinded		Adults	Sativex	Placebo	Pain Intensity (NRS); Adverse Events

CIM0029	Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain	Aron H. Lichtman, PhD, Eberhard Albert Lux, MD, Robert McQuade, PhD, Sandro Rossetti, MD, Raymond Sanchez, MD, Wei Sun, PhD, Stephen Wright, MD, MA, Elena Kornyeyeva,, and Marie T. Fallon	2018	yes	double blinded	yes	Adults	Nabiximols	Placebo	Pain Intensity (NRS); Adverse Events
CIM0060	A double blind, randomized, placebo-controlled, parallel group study of Sativex oromucosal spray (Sativex®; Nabiximols) as adjunctive therapy in relieving uncontrolled persistent chronic pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy.		2018	yes	double blinded	Parallel group trial	Adults	Sativex	Placebo	Pain Intensity (NRS); Adverse Events
CIM0073	A Secondary Analysis from a Randomized Trial on the Effect of Plasma Tetrahydrocannabinol Levels on Pain	Mark S. Wallace MD , Thomas D. Marcotte PhD , J.H. Atkinson MD , Hayley Treloar Padovano	2019	yes	double blinded	Cross over design	Adults	THC	Placebo	Pain Intensity (NRS); Adverse Events

	Reduction in Painful Diabetic Peripheral Neuropathy	Ph.D. , Marcel Bonn-Miller Ph.D.								
CIM0068	An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia	Tine van de Donka, Marieke Niestersa, Mikael A. Kowalb, Erik Olofsena, Albert Dahana,*, Monique van Velzena	2019	yes	double blinded	cross over	Adults, Female	Cannabis medical grade	Placebo	Pain Intensity (NRS); Adverse Events
CIM0032	Effect of Inhaled Cannabis for Pain in Adults With Sickle Cell Disease: A Randomized Clinical Trial	Donald I. Abrams, MD; Paul Couey, BA; Niharika Dixit, MD; Varun Sagi, BAS; Ward Hagar, MD; Elliott Vichinsky, MD; Mary Ellen Kelly, MPH; John E. Connett, PhD; Kalpna Gupta, PhD	2020	yes	double blinded	Cross over design	Adults, SCD	Inhaled Cannabis	Placebo	Pain Severity (VAS), AE
CIM0033	The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial	Almog S, Aharon, Peretz J, Vulfsons S, Ogintz M, Abalia H, Lupo T, Hayon Y, Eisenberg E	2020	yes	double blinded	Cross over design	Adults	Inhaled Cannabis	Placebo	Pain Severity (VAS), AE
CIM0034	The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief	Dixon H. Xu1, Benjamin D. Cullen,, Meng Tang5 and Yujiang Fang	2020	yes	double blinded	Cross over design	Adults	topical Canna	Placebo	Pain Intensit

	of Peripheral Neuropathy of the Lower Extremities							bidiol Oil		y (NRS)
CIM0036	In an exploratory randomized, double-blind, placebo-controlled, cross-over study, psychoactive doses of intravenous delta-9-tetrahydrocannabinol fail to produce antinociceptive effects in healthy human volunteers	Emmanuelle A. D. Schindler & Ashley M. Schnakenberg Martin & R. Andrew Sewell & Mohini Ranganathan & Anna DeFores t& Brian P. Pittman & Albert Perrino Jr & Deepak C. D'Souza	2020	yes	double blinded	Cross over design	Adults	THC IV	Place bo	Pain Severity (VAS)
CIM0037	Tetrahydrocannabinol and cannabidiol oromucosal spray in resistant multiple sclerosis spasticity: consistency of response across subgroups from the SAVANT randomized clinical trial	Sven G Meuth, Thomas Henze, Ute Essner, Christiane Trompke & Carlos Vila Silván	2020	yes	double blinded	Parallel group trial	Adults with MS	THC/CBD Spray	Place bo	Pain Intensit y (NRS); Adverse Events
CIM0039	Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial	Luca Eibach1, Simone Scheffel,2, Madeleine Cardebring Marie Lettau,M. Özgür Celik, Andreas Morguet, Robert	2020	yes	double blinded	Cross over design	Adults, HIV	Canna bivarin	Place bo	Pain Intensit y (NRS);

		Roehle and Christoph Stein								Adverse Events
CIM0046	Cannabinoids for Pain Control During Medical Abortion	Alyssa Covelli Colwill, R, Katie Alton, MD, MCR, Paula H. Bednarek, Lisa L. Bayer, Jeffrey T. Jensen,, Bharti Garg,, Kathleen Beardsworth,, and Alison Edelman,	2020	yes	double blinded	yes	Adults, Women	Dronabinol	Placebo	Pain Intensity (NRS)
CIM0059	Clinical pilot study to review the impact of perioperative administration of the synthetic cannabinoid nabilone in the context of spinal fusion surgery on the coping with surgery and the pain perception of patients with severely reduced quality of life	Dr. Astrid Pinsger-Plank, OA Dr. Philipp Becker	2020	yes	double blinded	Yes	Adults		Placebo	Pain Intensity
CIM0040	The CANBACK trial: a randomised, controlled clinical trial of oral cannabidiol for people presenting to the emergency department with acute low back pain	Bronwyn Bebee, David M Taylor, Elyssia Bourke, Kimberley Pollack, Lian Foster, Michael Ching, Anselm Wong	2021	yes	double blinded	yes	Adults	Oral Cannabidiol	Placebo	Pain Intensity (NRS); Adverse Events

CIM0041	Pain response to cannabidiol in induced acute nociceptive pain, allodynia, and hyperalgesia by using a model mimicking acute pain in healthy adults in a randomized trial (CANAB I)	Tobias Schneidera,*, Laura Zurbriggena, Markus Dieterlea, Eckhard Mauermanna, Priska Freib, Katja Mercer-Chalmers-Benderb, Wilhelm Ruppena	2021	yes	double blinded	Cross over design	Adults	Cannabidiol	Placebo	Pain Intensity (NRS); Adverse Events

JADAD SCORING

Jadad Score	
The Jadad score is often used to assess the methodological quality of controlled trials. Studies are scored according to the presence of three key methodological features of clinical trials, specifically randomization, masking, and accountability of all patients, including withdrawals. ONE point is given for a “yes” answer to each of the items, and ZERO point is given for a “no” answer to each of the items.	
Jadad Score Calculation	
Item	Score
J1. Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
J2. Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
J3. Was the study described as double blind?	0/1
J4. Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
J5. Was there a description of withdrawals and dropouts?	0/1
J6. Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1
J7. Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

Guidelines for Assessment	
Randomization	A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.
Double blinding	A study must be regarded as double blind if the word “double blind” is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

Withdrawals and dropouts	Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

JADAD SCORING SHEETS
VALIDATOR 1

Study Code	S1	S2	S3	S4	S5	S6	S7
J1. Was the study described as randomized (this includes words such as randomly, random, and randomization)?	1	1	1	1	1	1	1
2. Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated)?	0	0	0	0	1	1	1
J3. Was the study described as double blind?	1	1	1	1	1	1	1
J4. Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	1	1	1	1	1	1	1
J5. Was there a description of withdrawals and dropouts?	1	1	0	0	1	0	0
J6. Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0	0	0	0	0	0	0
J7. Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0	0	0	0	0	0	0
TOTAL	4	4	3	3	5	4	4

VALIDATOR 2

Study Code	S1	S2	S3	S4	S5	S6	S7

J1. Was the study described as randomized (this includes words such as randomly, random, and randomization)?	1	1	1	1	1	1	1
2. Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated)?	1	1	1	1	1	1	1
J3. Was the study described as double blind?	1	1	1	1	1	1	1
J4. Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	1	1	1	1	1	1	1
J5. Was there a description of withdrawals and dropouts?	1	1	1	1	1	0	1
J6. Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0	0	0	0	0	0	0
J7. Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0	0	0	0	0	0	0
TOTAL	5	5	5	5	5	4	5

VALIDATOR 3

Study Code	S1	S2	S3	S4	S5	S6	S7
J1. Was the study described as randomized (this includes words such as randomly, random, and randomization)?	1	1	1	1	1	1	1
2. Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated)?	1	1	1	1	1	1	1
J3. Was the study described as double blind?	1	1	1	1	1	1	1
J4. Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	1	1	1	1	1	1	1
J5. Was there a description of withdrawals and dropouts?	1	1	1	1	1	1	1

J6. Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0	0	0	0	0	0	0
J7. Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0	0	0	0	0	0	0
TOTAL	5	5	5	5	5	5	5

OVERALL QUALITY OF INCLUDED STUDIES

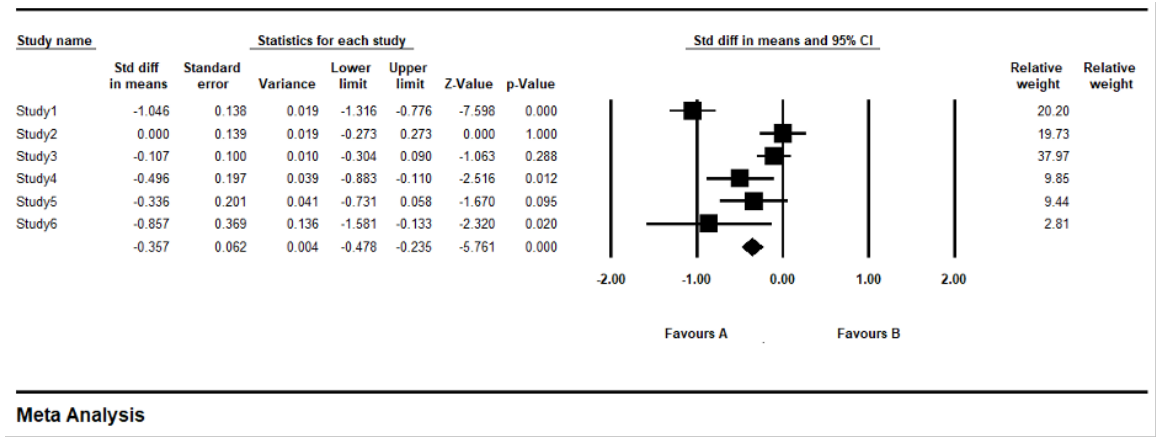
	V1	V2	V3	Average	Quality
Study 1	4	5	5	5	Good
Study 2	4	5	5	5	Good
Study 3	3	5	5	4	Good
Study 4	3	5	5	4	Good
Study 5	5	5	5	5	Good
Study 6	4	4	5	4	Good
Study 7	4	5	5	5	Good

META ANALYSIS FOR EFFICACY

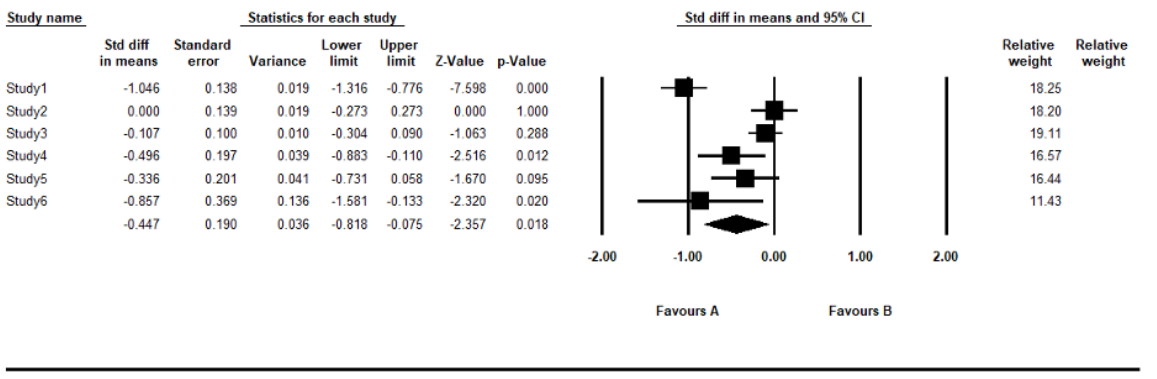
Model	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight
	Study1	-1.046	0.138	0.019	-1.316	-0.776	-7.598	0.000	20.20	18.25
	Study2	0.000	0.139	0.019	-0.273	0.273	0.000	1.000	19.73	18.20
	Study3	-0.107	0.100	0.010	-0.304	0.090	-1.063	0.288	37.97	19.11
	Study4	-0.496	0.197	0.039	-0.883	-0.110	-2.516	0.012	9.85	16.57
	Study5	-0.336	0.201	0.041	-0.731	0.058	-1.670	0.095	9.44	16.44
	Study6	-0.857	0.369	0.136	-1.581	-0.133	-2.320	0.020	2.81	11.43
Fixed		-0.357	0.062	0.004	-0.478	-0.235	-5.761	0.000		
Random		-0.447	0.190	0.036	-0.818	-0.075	-2.357	0.018		

Std diff in means and 95% CI: -0.250, -0.125, 0.000, 0.125, 0.250

FIXED EFFECT



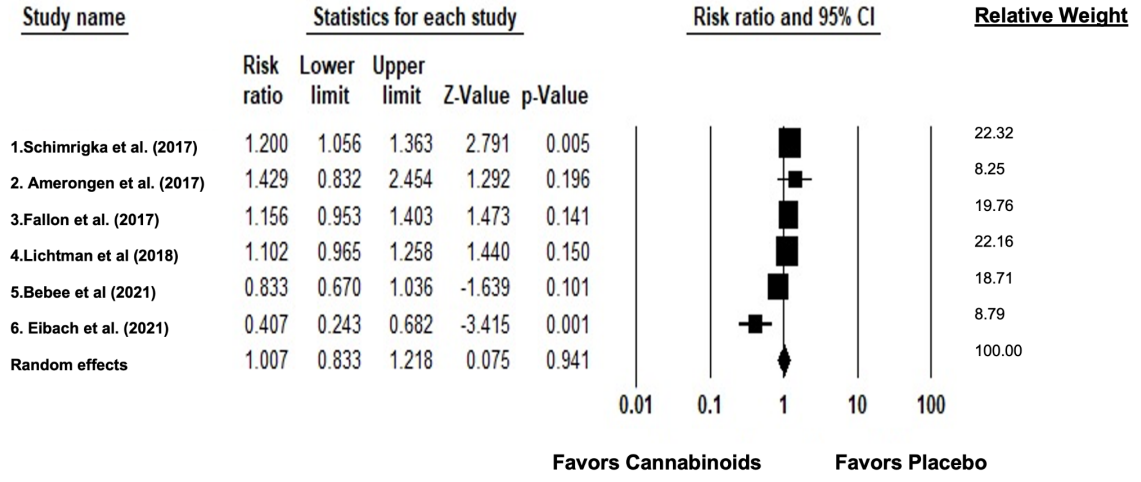
RANDOM EFFECT



Model	Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	6	-0.357	0.052	0.004	-0.478	-0.235	-6.761	0.000	40.169	5	0.000	87.553	0.178	0.146	0.021	0.422
Random	6	-0.447	0.190	0.036	-0.818	-0.075	-2.357	0.018								

META ANALYSIS FOR TOLERABILITY

Model	Study name	Statistics for each study					Risk ratio and 95% CI					Weight (Fixed)	Weight (Random)
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative weight	Relative weight
	Schimrigka	1.200	1.056	1.363	2.791	0.005						35.32	22.32
	Fallon et	1.429	0.832	2.454	1.292	0.196						1.97	8.25
	Lichtman et	1.156	0.953	1.403	1.473	0.141						15.46	19.76
	Meuth et al.	1.102	0.965	1.258	1.440	0.150						32.94	22.16
	Bebee et al	0.833	0.670	1.036	-1.639	0.101						12.14	18.71
	Eibach et	0.407	0.243	0.682	-3.415	0.001						2.17	8.79
Fixed		1.088	1.008	1.174	2.171	0.030							
Random		1.007	0.833	1.218	0.075	0.941							



Model	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	6	1.088	1.008	1.174	2.171	0.030	23.335	5	0.000	78.573	0.038	0.036	0.001	0.195
Random	6	1.007	0.833	1.218	0.075	0.941								

APPENDIX D

Certificate of Originality

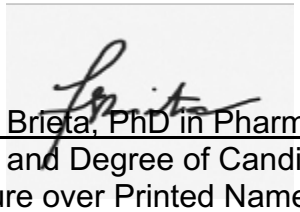
University of the Immaculate Conception
GRADUATE SCHOOL

CERTIFICATE OF ORIGINALITY

Date: June 28, 2022

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material to which to a substantial extent has been expected for award of any degree or diploma of a university or other institute of higher learning, except where due acknowledgement is made in the text.

I also declare that the intellectual content of this thesis/dissertation is the product of my work, even though I may have received assistance from others on style, presentation and language expression.



Ferlien Mae B. Brieta, PhD in Pharmacy — June 17, 2022
Name and Degree of Candidate — Date
(Signature over Printed Name)

Mohd Makmor Bakry — June 17, 2022
Name of Adviser — Date
(Signature over Printed Name)

CURRICULUM VITAE

FERLIEN MAE BAULA BRIETA,RPh.,PhD.
E-mail Address: fbaula@uic.edu.ph

Summary Statement:

- An experienced educator specialized in Higher Education Sciences with ten years of experience dedicated to holistic student development and promoting advocacy (research and community service) within the field of Pharmacy through education.
- Strong teaching and facilitating skills for diverse student, professional, and general audiences
- Extensive involvement in program research development dedicated to enhancement for Health Development.
- Proven ability to manage multiple projects while meeting challenging deadlines.

Academic Background

Post Graduate:	**University of the Immaculate Conception** **Doctor of Philosophy Major Pharmacy (May 2022)** University of the Immaculate Conception Dissertation *" Efficacy And Tolerability Of Selected Cannabinoids For Pain: A Systematic Review And Meta-Analysis"*
Graduate:	**University of the Immaculate Conception** **Master of Science in Pharmacy (May 2013)** Thesis "*Skill Performance and Clinical Core Competency Level of Clinical Pharmacy Graduates of the University of the Immaculate Conception: Basis for Curricular Enhancement*."
Tertiary:	**University of the Immaculate Conception** **Bachelor of Science in Clinical Pharmacy** (MARCH 2010) Award: **Best in Pharmaceutical Care**
Tertiary:	**University of the Immaculate Conception**

Bachelor of Science in Clinical Pharmacy
(MARCH 2008)
Award: **Cum Laude**

Awarded with Eligibility for Career Service Professional

Research Credibility (ejournals.ph)
Citations 22 h-index: 2

Work Experiences

1. University of the Immaculate Conception
College of Pharmacy and Chemistry
A. Associate Professor IV at University of the Immaculate Conception (2012 to present)
B. Research-in-Charge
Graduate School
A. MS Pharmacy Coordinator

2. *Davao Doctors Hospital*
Clinical Pharmacist April 2011 – June 2012
Serves as the immediate source of drug information at the nursing care units and other health professionals

3. Farmacia Southern Incorporated
Community Pharmacist (Supervisor) 2009- 2011

TRAINING AND SEMINARS ON PHARMACY/CHEMISTRY EDUCATION AND PRACTICE:

1. FIP PHARMABRIDGE PROGRAM SCHOLAR
October to November 2015 Monash University, Melbourne, Australia
Experience:
• Curriculum Review on BS Pharmaceutical Chemistry and BS in Clinical Pharmacy
• Consultation with Monash University Director and Faculty with regards to Classroom strategies to deliver efficiently Outcomes-Based Education
• Short immersion at Alfred Hospital and Austin Hospital for specialized training on/at Emergency Department, Antimicrobial Stewardship Program, Trauma, Medication Therapy Management.

2. Finisher, Six American College of Clinical Pharmacy Summits: Moving Mainstream Practice Toward Clinical Pharmacy

3. Speaker for "Thriving Hospital Pharmacy Excellence through Patient Centricity"

April 16, 2016 University of the Immaculate Conception

5. 11th Asian Conference on Clinical Pharmacy

June 24-27, 2011 PICC, Pasay City

AWARDS, TRAININGS AND SEMINARS ON SCIENTIFIC RESEARCH

1. Trainings on Systematic Review and Meta-Analysis:
    a. University Kebangsaan Malaysis, November 2020
    b. Philippine Pharmacy Association Davao, February 2021
2. Project Leader for DOST Research Fund on “Evaluation of Philippine Mango Peel Pectin as Tablet Binder for Formulated Sambong Tablet.”

3. DOST-RHRDC Mentorship Program Scholar - September to December 2018

4. Poster Presentor at Federation of Association of Pharmaceutical Association Congress 2018 (FAPA) at PICC, Manila, Philippines

5. Best Oral Presentor at Research Challenges in Multidisciplinary Innovation, October 5-8, South Korea

6. Orientation on the Use of Scopus and ScienceDirect database and Author Writeshop for Peer-Reviewed Journals-April 18, 2018

7. Workshop on Natural Products Chemistry: Appreciating FTIR Spectroscopy and Mass Spectrometry-November 29, 2017

8. Biostatistics Training: Introduction to Biostatistics and Research and Introduction to Data Management using Statistical Software-November 16-17, 2017

9. Basic Research Ethics Training-October 18-19,2017

10. PCHRD and DOST Research Writeshop for development of possible TUKLAS LUNAS Research-May 18-20, 2017

11. 6th Health R&D Expo Advisory Group: 3rd runner up Poster Presentation “Screening of Anticholinesterase Activity of Extracts from Ten Selected Indigenous Plants in Mindanao”- September 22-23, 2016

12. 2nd Certificate Course in Global Health Pharmacy: Redefining the Pharmacist’s Role in Global Health- August 3-5, 2017

13. 5th Health R&D Expo Advisory Group: 3rd runner up Poster Presentation “Hair

Growing Potential of Platito Plant (*Polyscias scutellaria*) Formulated as Lotion”- July 30-31 2015

14. Outstanding Institutional Research Achievement 2014-March 12, 2015

15. Certificate of Merit for International Research Presentation from Deans and Faculty Research Forum-March 11, 2015

16. Philippine Association of Institutions for Research, Inc on " Training Workshop on Case Study as an Approach to Qualitative Research"- February 16-17 2015

17. 2nd Asian Conference on Multidisciplinary Research in Higher Education; Certificate of Presentation, Best in Powerpoint Presentation November 26 to 28 2014 Marco Polo Hotel, Davao City

18. Oral and Poster Presentation at the National Convention Philippine Pharmacists Association, INC.-April 25, 2014

19. Embracing New Research Paradigms for Sustainability of Institutional Effectiveness March 12, 2014

20. 2nd Runner Up (National Academic Conference on Multidisciplinary Research)-February 6-7, 2014