The Use of Medical Cannabis in Clinical Practice

Arianne Kryskow
University of Maine, arianne.kryskow@maine.edu

Follow this and additional works at: https://digitalcommons.library.umaine.edu/etd

Part of the Nursing Commons

Recommended Citation
Kryskow, Arianne, "The Use of Medical Cannabis in Clinical Practice" (2021). Electronic Theses and Dissertations. 3527.
https://digitalcommons.library.umaine.edu/etd/3527

This Open-Access Thesis is brought to you for free and open access by DigitalCommons@UMaine. It has been accepted for inclusion in Electronic Theses and Dissertations by an authorized administrator of DigitalCommons@UMaine. For more information, please contact um.library.technical.services@maine.edu.
THE USE OF MEDICAL CANNABIS IN CLINICAL PRACTICE

By

Arianne B. Kryskow

BSN, University of Maine Fort Kent, 2018

M.Ed., University of Maine, 2010

A THESIS

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Science

(In Nursing)

The Graduate School

The University of Maine

December 2021

Advisory Committee:

Dr. Patricia Poirier, Professor of Nursing, Advisor

Dr. Eva Quirion, Professor of Nursing, Thesis Committee Member

Dr. Jordan Porter, Professor of Nursing, Thesis Committee Member
THE USE OF MEDICAL CANNABIS IN CLINICAL PRACTICE

By Arianne B. Kryskow

Thesis Advisor: Dr. Patricia Poirier

An Abstract of the Thesis Presented in Partial Fulfillment of the Requirements for the Degree of Master of Science (In Nursing) December 2021

Medical Cannabis is receiving renewed interest in clinical practice due to the gradual increase over the last few decades of cannabis legalization and high-quality research on the potential benefits of cannabis for treating a variety of conditions (NASEM, 2017; Nursing Care of the Patient, 2018). However, the pace of medical cannabis legalization and research are outpacing the training for medical providers, leaving gaps in their confidence and ability to safely guide patients using medical cannabis (NCSBN, 2018). Medical providers are increasingly fielding questions from patients regarding the use of medical cannabis for conditions commonly seen in clinical practice, but many are uncertain of if and how they should guide patients on this use. The aim of this research is two-fold: to assess current barriers to medical providers discussing medical cannabis with their patients; and to assess the impact a one-hour educational presentation can have on addressing these barriers and increasing the likelihood of providers engaging in discussions. Though the results of this research may be limited by the small sample size surveyed, they could highlight barriers present in clinical practice and indicate possible areas for future research in expanding cannabis education for medical providers.
ACKNOWLEDGEMENTS

I want to first acknowledge and thank Dr. Dustin Sulak, D.O. and his colleague Laurel Sheppard, FNP-BC for sharing their time, practice, and wealth of knowledge gained from over eleven years of clinical experience helping over 18,000 medical cannabis patients. They are true cannabis pioneers who paved the way for future providers, and I am forever grateful for their courage to help patients desperate for help including my own son. I also want to thank Dr. Sulak for giving me permission to use his Healer Medical Cannabis Training and Certification program and his new book *Handbook of Cannabis for Clinicians: Principles and Practice* which provided much of the material for this thesis and offers providers a wealth of knowledge and research on medical cannabis including treatment strategies and cautions based on Dr. Sulak’s extensive research and clinical experience.

I would also like to thank my advisor and lead for my thesis committee, Dr. Patricia Poirier, for sharing her time, structure, and academia wisdom that helped shape my passion into science and for believing in me and the topic even when others doubted. I would like to thank Dr. Eva Quirion and Dr. Jordan Porter for also being on my thesis committee and sharing their time, insight, kind support, and encouragement to share my passion but refine my voice.

Finally, I want to thank my husband, daughter, son, and best friend for their never-ending love and support, believing in my journey to study medical cannabis despite the many sacrifices needed to be made along the way. I also want to thank my son for inspiring this journey and allowing me to share his story of healing with medical cannabis with so many others in the hopes that they too may find relief from suffering and regain quality of life as he has. His courage, like many other pioneers and patients in the medical cannabis field, is changing the field of medicine bringing much-needed hope to many.
TABLE OF CONTENTS

ACKNOWLEDGEMENTS .................................................................................................................. iii

LIST OF TABLES .......................................................................................................................... viii

LIST OF FIGURES ......................................................................................................................... ix

Chapter

1. RATIONALE ................................................................................................................................. 1
   Legalization and Use of Medical Cannabis ............................................................. 1
   Research on Medical Cannabis ............................................................................... 2
   Support from Medical Community ....................................................................... 3
   Lack of Training for Medical Providers ................................................................. 3
   Impact on Patients Using Medical Cannabis ..................................................... 5
   Goal of Research: Assess Barriers and Impact of Intervention ...................... 6

2. BACKGROUND ON MEDICAL CANNABIS ......................................................................... 7

3. IMPACT OF SCHEDULE I STATUS ...................................................................................... 12
   Limits Research on Medical Cannabis ................................................................. 12
   Limits Access to Medical Cannabis .................................................................. 15

4. THE ENDOCANNABINOID SYSTEM ..................................................................................... 18
   Retrograde Signaling ............................................................................................ 19

5. PHARMACOLOGY OF CANNABIS ....................................................................................... 21
   Pharmacodynamics ................................................................................................. 21
   Pharmacokinetics ..................................................................................................... 23
   Side Effects ......................................................................................................................... 24
   Impacts on Side Effects ............................................................................................... 24
Recommendations for Doses/Ratios ................................................................. 42

Efficacy for Various Conditions .......................................................................... 43

Conclusive and Substantial Evidence Effective .................................................. 43

Moderate Evidence Effective ............................................................................... 43

Limited Evidence Effective .................................................................................. 43

Limited Evidence Ineffective ............................................................................... 43

Summary for Efficacy of Cannabis ...................................................................... 44

8. THE CURRENT RESEARCH ON MEDICAL CANNABIS .................................... 45

Resources for Research ....................................................................................... 45

Neuropathic Pain ................................................................................................. 46

Insomnia ............................................................................................................... 47

Epilepsy ............................................................................................................... 47

Opioid Use Disorder ............................................................................................ 49

Hepatitis C .......................................................................................................... 51

Other Neurological Conditions ............................................................................. 52

Cancer ................................................................................................................ 54

Summary of Current Research ............................................................................. 56

9. THESIS RESEARCH .......................................................................................... 57

Methodology ....................................................................................................... 57

Results ............................................................................................................... 58

Discussion ......................................................................................................... 60

Limitations of Study ........................................................................................... 60

Implications of Research .................................................................................... 62

vi
Conclusion .........................................................................................................................66
REFERENCES ....................................................................................................................67
APPENDICES ...................................................................................................................82
  Appendix A. Pre/Post Survey ...........................................................................................82
  Appendix B: Consent Form ...............................................................................................84
  Appendix C. Certificate of Analysis ................................................................................85
BIOGRAPHY OF THE AUTHOR ......................................................................................87
LIST OF TABLES

Table 10.1. Results from Pre/Post Survey .................................................................59
LIST OF FIGURES

Figure 8.1. Consensus-Based Recommendations for Tapering Opioids..........................5
CHAPTER 1
RATIONALE

Medical cannabis is receiving renewed interest in clinical practice due to the gradual increase in cannabis legalization and high-quality research on the potential benefits for treating a variety of conditions (NASEM, 2017; Nursing Care of the Patient, 2018). However, the pace of medical cannabis legalization, use, and research, is outpacing the training for medical providers leaving gaps in their confidence and ability to safely guide patients using medical cannabis (NCSBN, 2018).

Legalization and Use of Medical Cannabis

Despite being restricted by federal law, medical cannabis has become more prevalent in clinical practice as individual states pass their own regulations allowing its use (Nursing Care of the Patient, 2018). As of May 2021, medical cannabis is now legal in some form in 46 states and four territories with 36 states legalizing it for medical use and 18 of these also legalizing for recreational use, Maine included (State Medical Marijuana Laws, 2021). A 2019 study analyzing data from state registrations estimated that three million Americans use medical cannabis for relief for a variety of conditions, and this only includes those using medicinal cannabis with formal state authorization, not those without (Americans for Safe Access, 2019).

Cannabis is also the most commonly used illicit drug with a nationwide survey in 2105 estimating that 22.2 million Americans ages 12 and older used cannabis in the past 30 days, rising from 6.2% in 2002 to 8.6% in 2015, which is likely even higher today due to widespread increases in legalization (Bostwick et al., 2012; NASEM, 2017; Patel & Marhawa, 2021). In effect, millions of patients in clinical practice are using medical cannabis and providers need to
be discussing the risks and benefits of this use with their patients as they do with any other medicine.

**Research on Medical Cannabis**

High-quality clinical evidence exists and is rapidly emerging on the efficacy of medical cannabis for treating certain patient conditions, despite the restrictions in America from being classified as Schedule I (NASEM report, 2017; Sulak, 2021). Many other countries, including Canada, do not have the restrictions on cannabis research and have acknowledged its medical use and have provided much of this high-quality research (Understanding the New Access to Cannabis for Medical Purposes Regulations, 2016). Several of the randomized clinical trials (RCTs) studying the efficacy of medical cannabis for treating neurological conditions like multiple sclerosis (MS), chronic pain, insomnia, and post-traumatic stress disorder (PTSD) have been done with Nabiximols, a formulated cannabis extract with equal parts tetrahydrocannabinol (THC) and cannabidiol (CBD) legal in the United Kingdom and Europe for the treatment of MS and spasticity, which is currently awaiting approval in the United States as Sativex (*Healthcare Professionals [GW]*, n.d.; Russo et al., 2018). Other RCTs have used Epidiolex, a purified version of plant-based CBD legal in the United Kingdom and European Union for the treatment of severe epilepsy. In 2018, this led to recent FDA approval in the United States for the same use (*Healthcare Professionals [GW]*, n.d.; Russo et al., 2018).

In 2015, the World Health Organization (WHO) produced one of the most prominent reports summarizing the clinical evidence for medical cannabis concluding that cannabis should be removed from scheduling to allow for research. In 2020, the United Nations approved the report (*Current Scheduling Regulations [UN]*, 2021; Madras, 2015). The second most prominent and comprehensive report came from the National Academies of Science, Engineering, and
Medicine (NASEM), which charged a committee with doing a rigorous review of the scientific research published from 1999 to 2017 about the health impacts of cannabis and cannabinoids and their therapeutic effects and risks for harm. The committee considered more than 10,000 high-quality studies to reach its nearly 100 conclusions, determining that 86% of the conditions patients use medical cannabis for are supported by strong evidence and that scheduling of cannabis should be reviewed to allow for more rigorous and quality research (NASEM, 2017; Rapaport, 2017).

**Support from Medical Community**

Even before the WHO and NASEM reports concluded there was strong clinical evidence to support the use of medical cannabis, most medical providers already supported its use. A 2013 poll in the New England Journal of Medicine found that more than 75% of US physicians think medical cannabis is a safe and effective treatment (Adler, 2013). The American Medical Association (AMA), the American College of Physicians (ACP), and the American Academy of Pediatrics (AAP) have all released statements of support calling for cannabis scheduling to be reviewed to allow for research, with some medical associations like the ACP and AAP openly acknowledging the evidence for medical use and requesting more clinical trials and pharmaceutical development (NORML, 2015). However, this support from the medical community has not translated to increased training on medical cannabis for providers.

**Lack of Training for Medical Providers**

Many providers do not realize the distinction between medical use and recreational use, where the goal of medical cannabis is not impairment but to improve health and function using measured doses and controlled ratios of THC:CBD with much less risk of impairment or abuse than recreational use (Cerdá, 2020; Williams et al., 2017). Some medical programs like the
National Council of State Boards of Nursing have recently updated their guidelines requiring that medical cannabis education be included in curriculum to provide nurses with “principles of safe and knowledgeable practice to promote patient safety when caring for patients using medical [cannabis]” (NCSBN, 2018; Nursing Care of the Patient, 2018). However, the requirement for medical cannabis education is not the case for all medical curricula and, even when it is required, has not often transferred to actual practice. A 2018 national survey of US medical school curriculum deans, Washington University fellows and residents, and Association of American Medical Colleges Curriculum Inventory database found 67% of the deans and 90% of the residents reported graduates were “not at all prepared” to recommend medical cannabis, while 85% reported “receiving no formal education” (Evanoff et al., 2018).

This lack of medical training on cannabis may be a significant barrier to providers discussing the use of medical cannabis with their patients using it or those wanting to use it. A survey of a large comprehensive cancer center in Seattle found that although 21% of the patients were using cannabis to treat their symptoms from chemotherapy, 74% surveyed wanted more information and guidance on cannabis from their health care team, yet only 15% reported they received it (Pergram et al., 2017). This survey reveals there may be many patients wanting to discuss medical cannabis with their providers, but unfortunately the providers are not doing this.

A 2018 survey of medical oncologists in Minnesota set out to assess the possible barriers that may be preventing providers from discussing and recommending medical cannabis with their patients. There were 14 questions designed to identify the providers’ current practices regarding medical cannabis, as well as their knowledge and attitude towards it. Overall, the study revealed great support among providers for exploring medical cannabis with their patients, however, very few oncologists reported they had formal training on cannabis, with 36%
reporting they were “not or not at all confident” discussing the risks and benefits, and 85% reporting they wanted more education on cannabis (Zylla et al., 2018). Other perceived barriers were, in order of greatest to smallest barriers: concerns about cost, inadequate research, pros/cons of use, FDA approval, risk of abuse/misuse, quality of product, legality for prescriber and patient, social stigma, and the health group not allowing or supporting discussion of medical cannabis (Zylla et al., 2018). Though this survey represents a specialized segment of the medical field, it reveals that lack of education on these topics may be a significant barrier to providers discussing medical cannabis with patients and suggests that providing them with the necessary education may help bridge this gap.

**Impact on Patients Using Medical Cannabis**

Many medical providers are increasingly fielding questions from patients using cannabis for a multitude of conditions commonly seen in clinical practice, such as chronic pain, insomnia, neuropathies, anxiety, arthritis, nausea/vomiting, irritable bowel syndrome (IBS), opioid reduction, etc. and are uncertain how to answer these questions (Nursing Care of the Patient, 2018). With Maine’s recent legalization of cannabis for recreational use in adults, questions about medical cannabis are expected to likely increase.

Many patients are using medical cannabis and in need of guidance from their providers. However, most providers lack the education and confidence to be able to discuss the risks/benefits of cannabis and guide their patients. This leaves millions of patients on their own experimenting trying to determine the right type of cannabis, dose, method of administration, frequency, and duration, to find relief for their suffering and various conditions.
**Goal of Research: Assess Barriers and Impact of Intervention**

The goal of this thesis therefore is two-fold: one, to assess current barriers in clinical practice to medical providers discussing and guiding medical cannabis use with their patients; and two, to explore the impact a brief educational intervention can have on addressing these barriers and increasing the likelihood of providers engaging in these discussions. Though the results of this study may be limited by the small sample size surveyed and the limited duration of the educational training, it could highlight barriers present in general clinical practice and indicate possible areas for future research in expanding cannabis education for all medical providers.
CHAPTER 2

BACKGROUND OF MEDICAL CANNABIS USE

The use of cannabis for medical purposes has deep roots dating back over 5,000 years with the earliest written reference in 1500 BC in the Chinese Pharmacopeia then spreading to Egypt, India, Africa, and by the 1850’s into the Western world and listed in the US Pharmacopeia as a tincture for numerous afflictions including neuralgia, cholera, dysentery, alcoholism, opiate addiction, incontinence, convulsions, insanity, menstrual bleeding, insomnia, anorexia, dyspepsia, etc., (Bostwick, 2012; Ryan et al., 2021; The Report from the National Commission, 1972). A comprehensive review of the use of medical cannabis in America shows it held “a prominent position in the history of medicine, recommended by many eminent physicians for numerous diseases” noted particularly for its analgesic, anticonvulsive, anxiolytic, and antiemetic properties, was commonly sold over the counter, and was the 3rd-4th most common ingredient in drug preparations, but through the decades moved from “a legal and frequently prescribed status to illegal, driven by political and social factors rather than science” (Baron, 2015; Bearman et al., 2018).

There are many books and documentaries documenting these factors as well as the racism behind the campaign in the 1930’s to criminalize cannabis stemming from an anti-minority sentiment growing in the southern and western states where there was an influx of immigrants from Mexico and “Negro” jazz musicians who commonly used cannabis (Earleywine, 2005; Ryan et al., 2021; Weed the People, 2018). The head of the newly formed Federal Bureau of Narcotics, Henry Aslinger, stoked racist fears citing false instances of minorities committing crimes on cannabis saying “marijuana is the evil Mexican plant that drives you insane,” “makes darkies think they’re as good as white men,” and “causes white women to seek sexual relations
with Negroes” though he admitted in private memos that these accusations were all fabricated (Earleywine, 2005; Wing, 2014). Aslinger’s campaign was propagated by William Hearst who owned most of the newspapers at the time and had major investments in the timber and paper industry which feared competition from hemp that required 75% less chemicals to make paper than wood pulp (Bearman, 2017; Earleywine, 2005; Wing, 2014).

The campaign to criminalize cannabis was successful and led to the passage of the “The Marijuana Tax Act” in 1937 which required anyone using the plant to register and pay a tax or risk $2,000 fine or 5 years imprisonment (Zuardi, 2006). The American Medical Association opposed this act explaining that there was currently no drug available to replace cannabis for many of the conditions it was used to treat. Science was ignored, and cannabis was no longer sold over the counter and was removed from the pharmacopeia soon after in 1941 (Baron, 2015; NCSBN, 2018; The Report from the National Commission, 1972).

In 1970, The Controlled Substances Act (CSA) was passed, placing cannabis temporarily in the list of Schedule I Controlled Substances with “high potential for abuse” and “no medical use” pending a commission’s investigation. (Controlled Substances Act [CSA], 1970). In 1972, the commission appointed by President Nixon, known as the Shafer Commission, thoroughly reviewed the research and released its report two years later “Marijuana: A Signal of Misunderstanding, the Report of the US National Commission on Marijuana and Drug Abuse.” The report concluded that cannabis had medical use, was safe, and should be removed from Schedule I saying: “the volume of information available on the medical application of cannabis is considerable,” “the actual and potential harm of use of the drug is not great enough to justify intrusion by the criminal law,” and recommended that “the possession of marijuana for personal use no longer be an offense” (The Report of the National Commission, 1972). President Nixon
ignored these recommendations and cannabis remains Schedule I to this day, continuing the prohibition of medical cannabis federally and effectively prohibiting medical practitioners from prescribing cannabis (NCSBN, 2018).

Cannabis use remained restricted until 1996, when voters in California approved the first legalization of medical cannabis. However, the federal government opposed this proposition and threatened to revoke the prescription-writing abilities of doctors who prescribed or recommended cannabis (Ryan et al., 2021). In 2000, this policy was challenged by a group of physicians who prevailed in court with the ruling deciding that physicians could recommend—but not prescribe—medical marijuana, as it was protected speech by the First Amendment (Conant vs McCaffrey, 2000). This ruling was later defended in 2002 with a decision from the Ninth Circuit Court of Appeals confirming that doctors could not be punished by the federal government for discussing or recommending medical cannabis, and prohibiting the federal government from “revoking a physician's license to prescribe controlled substances or conducting an investigation of a physician that might lead to such revocation, where the basis for the government's action is solely the physician's professional 'recommendation' of the use of medical marijuana.” (Conant HIV AIDS vs Walters DEA, 2002).

Since these rulings and the first legalization of medical cannabis, there has been a steady increase in cultural acceptance of cannabis use in America with many other states following California’s lead and Maine being the fifth state to legalize medical use (State Medical Marijuana Laws, 2021). As of May 18, 2021, medical cannabis is now legal in some form in 46 states, the District of Columbia, Guam, the Virgin Islands, and Puerto Rico, with 18 states also legalizing cannabis for adult recreational use, including Maine (State Medical Marijuana Laws,
Many other countries have not had the same scheduling restrictions to cannabis research and have made major advancements impacting medical use. A most important discovery was in 1992 in Israel when Dr. Raphael Mechoulam and a team of scientists discovered the endocannabinoid system (ECS) after isolating the first endogenous cannabinoid neurotransmitter they named ‘anandamide,’ meaning ‘bliss’ in Sanskrit. The discovery of the ECS significantly expanded the research on cannabis and led to a deeper understanding of the pharmacology of cannabis, the exogenous cannabinoid which mimics endocannabinoids (Pertwee et al., 2006). By 2003, there was enough research on cannabinoids for the U.S. Department of Health and Human Services to receive a patent US 6630507 B1 for the therapeutic use of "cannabinoids as antioxidants and neuroprotectants," explaining that “cannabinoids have been found to have antioxidant properties…” and “particular application as neuroprotectants…” in the treatment of “acute ischemic neurological insults,” “chronic neurodegenerative diseases,” and “oxidation associated diseases” (Hampson et al., 2003).

In 2015, the World Health Organization published a prominent report examining the evidence of cannabis research and determined cannabis had many medical uses (Madras, 2015). Soon after, the WHO’s Expert Committee on Drug Dependence recommended removing cannabis from scheduling, acknowledging its medical utility and the need for further research, which the United Nations recently approved in 2020 (Current scheduling recommendations [UN], 2021).

In America, legislation to remove cannabis from scheduling has been proposed multiple times throughout the decades and most recently in August 2021 with the “Cannabis
Administration and Opportunity Act” advocating to remove all cannabis from scheduling to allow regulation and tax (Fandos, 2021). It is estimated that 70% of the American public now support the legalization of cannabis, and it is a matter of time before legislation to make it federally legal is passed (Fandos, 2021).
CHAPTEER 3

IMPACT OF SCHEDULE I STATUS

Limits Research on Medical Cannabis

The effects of cannabis being classified as federally illegal are wide and have had a significant impact on society medically as discussed below. It is also important to be mindful of the social impacts as well. The aggressive enforcement of cannabis possession laws continues to unfairly prejudice minorities and is well documented by the American Civil Liberties Union who report people of color are still four times as likely as whites to be arrested for cannabis possession, despite using the drug at the same rate, and are also disproportionately targeted by SWAT teams, often resulting in violence (ACLU, 2018).

The medical impacts of the illegal status of cannabis are significant as this has considerably impeded the advancement of research in the United States. Research is still possible and has also been done in other countries, but restrictions from the federal government limits the amount of the randomized-controlled trials approved in America, considered the gold standard in medicine, which therefore limits the amount of evidence-based information providers need to guide their practice (NASEM, 2017; Ryan et al., 2021). Most funding for cannabis research comes from the National Institute of Drug Abuse (NIDA) whose mission is to “advance science on the causes and consequences of drug use and addiction.” It is therefore not surprising that most of the cannabis studies approved are those investigating the harms of cannabis (94% of all cannabis studies approved in 2016) and less than one fifth of the studies approved are those investigating the therapeutic properties (6% of all cannabis studies approved in 2016) (MacDonald, 2016; NASEM, 2017).
Even when the government does approve cannabis studies, the process to obtain cannabis for research is known to be “cumbersome and unlike any other procedures used for drug research” (NASEM, 2017; NCSBN, 2018). In fact, the government studies require researchers to use either the synthetic approved versions of THC (Nabilone and Drabinol) or cannabis from their government supply from the University of Mississippi, both of which have proven to be less effective and lower quality than most medical cannabis (Hellerman, 2017; MacDonald, 2016). In 2016, tests on the government cannabis showed they were contaminated with mold and yeast and had lower amounts of cannabinoids and lower potency. For example, the potency of THC was almost two-three times lower than medical cannabis, ranging from 3-7% with the highest level of THC at 12.4% compared with medical strains ranging from 18.7-35% (Hellerman, 2017; MacDonald, 2016). This means that results from government funded studies with lesser quality cannabis may offer little to no insight into the actual therapeutic and adverse effects of medical cannabis and are less applicable in clinical practice.

As well, the research often does not encompass all available formulations of cannabis used in medical use and often does not indicate specific dosages, duration, route, or which chemovar was used -- meaning ‘chemical variety’ in the plant, also called ‘strains,’ which vary considerably in their content and ratio of cannabinoids (NCSBN, 2018; Ryan et al., 2021). The ratio of THC:CBD is a critical differentiating factor in medical use and a major contributor to ensuring cannabis is therapeutic rather than impairing (Sulak, 2021). Though both cannabinoids have analgesic and neuroprotective properties, they do differ -- THC has more potent analgesic, anti-spasmodic, and sedative effects and can temporarily dull short-term memory (helpful for severe pain, insomnia, and PTSD) while CBD has more potent anti-inflammatory, anti-convulsive, and anxiolytic effects and can increase focus and concentration (helpful for
inflammatory pain, anxiety, ADHD) (Pertwee et al., 2006; Russo et al., 2018; Sulak, 2021).
Although there are over 25,000 studies describing the safety and efficacy of cannabis for treating
certain conditions, more RCTs are needed to provide the evidence-based specificity in which
dose/ratio/duration is best for which conditions to help providers understand how to apply this
research to clinical practice (Ware et al., 2015).

Fortunately, there are some high-quality clinical trials and resources providers can look to
for current guidance from practicing expert cannabis clinicians like the Society of Cannabis
Clinicians, a nonprofit educational and scientific society of physicians and health care
professionals dedicated to the education and research of medical cannabis use, offering a
collection of course, webinars, and research studies to guide clinical decision making, where all
articles are vetted to ensure only rigorous, unbiased, non-commercial studies (SCC Library,
n.d.). The Medical Cannabis Institute also offers accredited online medical cannabis education
for healthcare professionals and state-specific certification, developed by TMCIGlobal in
collaboration with the Society of Cannabis Clinicians (TMCI.com, n.d.). Dr. Dustin Sulak, D.O.,
an internationally renowned cannabis clinician with over eleven years in clinical practice treating
18,000+ medical cannabis patients also has a cannabis certification program and free training for
providers and patients with many articles and monthly webinars reviewing the latest research
(Healer.com). Dr. Sulak also recently released a book, the *Handbook of Cannabis for Clinicians:
Principles and Practice* which provides a wealth of knowledge and research on medical cannabis
for a multitude of conditions, including treatment strategies and cautions based on his extensive
research and clinical experience (Sulak, 2019; Sulak, 2021). However, most medical providers
may be unaware of these resources to educate themselves on medical cannabis use.
**Limits Access to Medical Cannabis**

The illegal status of cannabis has also significantly impacted access to quality medicine with access varying widely depending on which state patients live in and what their regulations or qualifying conditions are (NCSBN, 2018). The Journal of Nursing Regulation lists some of the most common qualifying conditions across all MMPs that patients receive certifications from various states to use cannabis for: chronic pain, insomnia, neuropathies, nausea/vomiting, ALS, Alzheimer’s, Parkinson’s, mood and anxiety disorders, arthritis, fibromyalgia, cachexia, cancer, Crohn’s, ulcerative colitis, IBS, epilepsy, seizure, glaucoma, Hepatitis C, HIV/AIDS, migraines, MS, muscle spasms, PTSD, sickle cell disease, terminal illness, opioid use disorder (NCSBN, 2018). Although this list gives an idea of the wide span of therapeutic uses patients are utilizing cannabis for, not all these conditions are legal in all states (NCSBN, 2018). These discrepancies restrict access to medical cannabis depending on which conditions are approved, even if the patients do live in a state where it is legal. Patients in Maine have easier access to medical cannabis than most since 2017, when recreational use was legalized and medical use was amended to no longer require providers to state a qualifying condition for medical certification. Instead, providers only need to deem that the patient may benefit from use and that the risks and benefits were discussed, with the law stating that a provider need only state that “in their professional opinion, a qualifying patient is likely to receive therapeutic or palliative benefit from the medical use of marijuana to treat or alleviate the patient’s medical diagnosis” (*Maine Medical Use of Marijuana Act*, 2017)

The few forms of cannabis available to patients who live in states without medical use or approved qualifying conditions are the FDA approved synthetic isolated cannabinoids (i.e., Schedule II ‘Nabilone’ and ‘Dronabinol’, synthetic isolates of THC and ‘Epidiolex’, a purified
isolate of CBD) proven to be less effective than whole plant cannabis (Sulak, 2021). The higher efficacy of the whole plant cannabis is due to the synergistic effects of all 550 phytocompounds within the plant which includes 120 identified cannabinoids and several different terpenes known as ‘essential oils’. This synergistic effect is known as the ‘Entourage Effect’ and is well-established by research showing these phytocompounds have even more potent effects when administered together than they do alone (Russo, 2011; Pertwee, 2008). A recent meta-analysis comparing Epidiolex to whole plant CBD-rich extract which contains all the phytoconstituents of the plant, including a small amount of THC found that 36% of patients improved with the isolate compared to 71% with the whole plant, plus those using Epidiolex had to use dosages four times higher leading to more adverse effects compared to those using whole plant CBD (Pamplona et al., 2018). However, when patients live in states where medical use is not legal or end up in hospitals that refuse to allow patients to use their medical cannabis due to fears of losing federal funding, these lower synthetic replacements are often the only options patients have (Sulak, 2021).

Whole plant CBD is currently available to patients now that the CSA was amended to de-schedule strains of cannabis with high concentrations of CBD with less than 0.3% THC (Ryan et al., 2021). However, the market is largely unregulated like supplements and, without being federally legal and FDA approved, is not subject to the same quality and safety standards as most prescription drugs (NCSBN, 2018). This has led to inaccurate labeling of many CBD products. A 2017 JAMA study found only 30% of CBD sold online contained percentages of CBD within 10% of that labeled, with 26% containing little to no CBD, and almost half mislabeled and containing contaminants (Bonn-Miller at al., 2017). Some companies have also been misleading in their labels, for example labeling bottles by the amount of ‘hemp extract’ in the bottle (i.e., 75
mg) rather than the amount of active cannabinoid CBD (i.e., less than 14 mg) (Bonn-Miller et al., 2017). This mislabeling considerably changes the amount of CBD patients are getting with each dose, leading to inconsistent and reduced therapeutic effects, if any.

Many patients and providers may not be aware of ways to ensure that cannabis products sold online or in dispensaries contain safe and effective contents. More responsible companies will require their products to be tested in an independent laboratory, known as ‘third-party testing,’ to determine the exact content/amounts of each cannabinoid and terpene in each batch and to ensure there are no contaminants like heavy metals, solvents, pesticides, yeast, or mold. Patients aware of this laboratory testing can ask companies for the certificate of analysis, (COA) often available on the label with a QR reader or listed on the website, to know exactly what their cannabis product contains and to determine if it is the right product for their needs (see Appendix A: COA). Many patients are not aware of the need to look at the COA and do not understand that without federal oversight their product may not be safe or effective (Bonn-Miller et al., 2017; Sulak, 2021)

In summary, the current scheduling of cannabis as federally illegal continues to restrict high quality research for providers and access to high-quality medicine for patients. Without evidence-based protocols, patients are left on their own to experiment and figure out doses and ratios of medicine. Without federal oversight on products, it is also up to the patient to navigate the unregulated cannabis market to ensure they are getting safe, consistent medicine of high quality.
CHAPTER 4

THE ENDOCANNABINOID SYSTEM

Before trying to understand the complex nature of the effects of cannabis, it is important to have a deeper understanding of the endocannabinoid system (ECS) and its’ ability to produce bidirectional effects, or opposite effects. The ECS is comprised of numerous endocannabinoids (most notably 2-AG and AEA/anandamide) and the numerous cannabinoid receptors it binds to (most notably CB1 and CB2) found throughout the body but most concentrated in the nervous system (Pertwee, 2008). The ECS is one of the most important physiologic systems in the body and performs different tasks in different tissues, but with the same overarching goal: homeostasis, maintaining balance inside bodies despite fluctuations in external environment (Donvito et al., 2018; Parsons & Hurd, 2015). The ECS is involved in processes modulating pain, inflammation, mood, appetite, sleep, memory, blood pressure, etc. and is most known for helping us relax, eat, sleep, forget, and protect our bodies from injuries or illness (DiMarzo et al., 1998; TMCI, n.d.).

The endocannabinoids are synthesized on demand from eicosanoids and have mostly local effects and short half-lives, degraded by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (TMCI, n.d.). Arachidonylethanolamide (known as AEA or anandamide) is a full agonist at TRPV1 and partial agonist at CB1/CB2, while 2-Arachidonylglycerol (2-AG) is a full agonist at CB1/CB2 and is the most commonly expressed endocannabinoid in the brain (TMCI, n.d.). These endocannabinoids are known for their neuroprotective and neuromodulating effects -- THC mimics both AEA and 2-AG while CBD modulates them. (Russo et al., 2018; Sulak, 2021).
**Retrograde Signaling**

The main receptors these endocannabinoids bind to are CB1 receptors found mostly in the central nervous system but also in organs (heart and lungs), muscles, glands, gonads, and connective tissue (Elphick & Egertová, 2001). CB1s are the most highly expressed GPCRs in the brain and are located pre-synaptically on the neuron (Pertwee, 2008). This pre-synaptic location of the receptors means the signaling for ECS is retrograde, backwards -- a major contributor to the wide variety of and sometimes opposite therapeutic effects cannabis can have (Pertwee, 2008). Cannabinoids can travel backward to bind with CB1 on the presynaptic neuron where they can inhibit the neuron’s release of neurotransmitters, essentially acting as a negative feedback loop for neurotransmission (TMCI, n.d.; Zou & Kumar, 2018). For example, if there is too much activity in the brain, agonists at CB1 could limit the release of excitatory glutamate but if there is not enough activity, it could limit the release of inhibitory GABA instead -- this explains the ability of cannabis to both excite and sedate (Sulak, 2021). CB2 receptors are found mainly in the immune system and spleen but also the liver, pancreas, bones, and skin. CB2 agonists are involved in immune cell migration and can inhibit the release of pro-inflammatory cytokines (Pertwee, 2008; TMCI, n.d.). There are no cannabinoid receptors located in the brain-stem cardiorespiratory centers which is why cannabis has no lethal dose as it cannot shut down breathing or heart rate, like opioids can (Glass, 1997; Sulak, 2021).

Many disease processes such as migraines, fibromyalgia, and IBS are thought to be due to a deficiency in our ECS, which can be impaired by chronic stress and poor diet, especially the standard American diet, which is low in Omega 3 fatty acids, a key ingredient needed to build endocannabinoids. (McPartland et al., 2014; Russo et al, 2018; Sulak, 2021;). Research on modulating the ECS to improve health shows that levels of endocannabinoids can be increased
naturally through a healthy lifestyle, most notably diets rich in vegetables and omega-3s, regular exercise, and stress-reduction strategies such as yoga and meditation (McPartland et al., 2014). Clinical studies support this and suggest the runner’s high may be due to increased endocannabinoid levels rather than endorphins, where 30 minutes running produced higher levels of anandamide, more quickly than endorphins, and stayed elevated long after the endorphins were gone (Heyman et al., 2012; Sparling et al, 2003). However, animal studies on forced long-term exercise showed endocannabinoid levels increased but stayed elevated to the point where CB1 receptors downregulated, giving insight into how conditions that put a lot of stress on our bodies might lead to a deficiency of our ECS (McPartland et al., 2014). The other way to support the ECS is with exogenous supplementation through cannabis which contains phytocannabinoids that mimic endocannabinoids.
CHAPTER 5

PHARMACOLOGY OF CANNABIS

The cannabis plant contains over 550 phytocompounds, 120 of which are identified as phytocannabinoids, and the chemovar (chemical variety) of each plant can vary considerably depending on its chemotype -- type of cannabinoids within and the amounts or ratios of each (Nahler et al., 2019). When selecting a chemovar for medical use, the most important compounds to look at are THC and CBD (their amounts and ratio to each other), followed by the kind of terpenes which can also influence the plant’s ability to sedate (i.e., linalool, myrcene) or stimulate (i.e. limonene) (Russo et al, 2018; TMCI, n.d.).

**Pharmacodynamics**

THC is the cannabinoid most known for cannabis’ psychoactive effects, but it is also a powerful medicine responsible for some of the most common effects cannabis is used for: analgesic, anti-spasmodic, anti-emetic, induces sleep, and appetite stimulant effects. It can also cause significant side effects (i.e., hypotension, tachycardia, and euphoria) and significant adverse effects in higher doses (anxiety/paranoia, impaired short-term memory, and delayed motor coordination) (TMCI, n.d.). Though an excess dose of THC cannot be lethal, it can be very unpleasant and cause rapid heart rate, mental confusion, and paranoia that can last from 4-24 hours. It is generally associated with ingestion of edibles that have a delayed and erratic onset leading some patients to ingest higher doses than needed (Sulak, 2021). This is uncommon in medical use that more carefully controls the concentration of THC and uses CBD that mitigates the peak and onset of THC. Cannabis clinicians recommend mitigating the intoxication with CBD 1-2 times the dose of THC that was ingested (Russo & Guy, 2006; Sulak, 2020).
The other major phytocannabinoid that THC works best in conjunction with is CBD, which is rapidly gaining interest in medical use due to its wide variety of therapeutic properties and high safety profile (TMCI, n.d.). CBD is non-intoxicating so is not regulated internationally and is often prescribed in low doses in other parts of the world for its neuroprotective antioxidant properties (Sulak, 2019). CBD is a negative allosteric modulator at CB1, meaning it can prevent THC from binding which is how CBD mitigates the peak and side effects of THC, a key component to medical use (Pertwee, 2008; Russo et al., 2018; Sulak, 2021). Studies in cell models show that CBD also has over 65 pharmacologic targets which explains its wide variety of effects: it is a partial agonist at CB2 which is likely how CBD reduces inflammation and modulates the immune system; an indirect agonist at 5-HT1A which is likely how CBD reduces anxiety, nausea, and improves focus; an agonist at TRPV1 so can also reduce pain; an antagonist to the mu-opioid receptors which is likely how CBD can reduce opioid cravings and use; also can inhibit uptake of neurotransmitters NE, DOP, SER, GABA, and anandamide which is likely how CBD is beneficial for many mental health issues (Ibeas et al, 2015; Nahler et al., 2019; Russo et al., 2018). CBD is also well-tolerated with the only side effects being decreased appetite and, at higher doses > 100 mg/day, can cause sedation and diarrhea. (Russo et al., 2018; Nahler et al., 2019).

There is also promising research on the other phytocannabinoids as well, especially THCA and CBDA, the non-intoxicating precursors to THC and CBD that exist in the raw plant before it is decarboxylated. These have been shown to have powerful therapeutic effects of their own (anti-inflammatory, anti-emetic, anti-neoplastic) in minute amounts and contribute to the entourage effect, enhancing the effects of THC and CBD (Moreno-Sanz et al., 2016; Russo et al., 2011; Sulak, 2021). Clinical evidence is showing they have much higher bioavailability than
THC and CBD, up to 5-10 times the amount (Sulak, 2020). In clinical practice many elderly patients will use THCA and CBDA by steeping a pea-sized piece of the raw flower in tea for a few minutes to get the anti-emetic and anti-inflammatory effects of the plant without the psychoactivity (Sulak, 2021).

**Pharmacokinetics**

The pharmacokinetics of medical cannabis vary greatly, especially with different methods of administration, with oromucosal being the most preferred in medical use and inhalation only recommended for acute relief, with a flower vaporizer only and no smoking (Sulak, 2021; TMCI, n.d.). The absorption for oromucosal ranges from 6-15% which is less than absorption with inhalation which ranges from 10-35%. Oromucosal bioavailability, however, can be enhanced up to five times with ingestion of food containing fats since both THC and CBD are lipophilic compounds, and it can also be enhanced by keeping it sublingual or buccal for 1-2 minutes before swallowing. The peak concentration for oromucosal can vary widely from 1-6 hours but the duration of effects can last up to 12 hours, on average 6-8 hours. This makes sublingual delivery ideal for medical use, able to be dosed two to three times a day.

Once cannabis is swallowed it is metabolized in the liver by the cytochrome P450 enzymes with the most common for both THC and CBD being CYP3A4 and CYP2C9, and 2C19 for CBD, with the average half-life of THC being 10-17 hours and CBD being 1-2 days. Drugs that are metabolized by the same enzymes cannabis is such as warfarin and anti-epileptic drugs like clobazam should be monitored as doses may need to be decreased with regular use of medical cannabis (Damkier et al., 2018). Providers can screen for drug-drug interactions on Medscape by using the terminology of the FDA approved synthetic versions of cannabis such as ‘Nabilone’ for THC and ‘Epidiolex’ or cannabidiol for CBD (Sulak, 2021).
Elimination is slow due to accumulation in adipose tissue and some studies show cannabis can be re-released with exercise even weeks later termed the ‘depot effect.’ However, 80-90% is excreted within five days, with 20-35% eliminated in urine and 65-80% eliminated in feces. Although inactive metabolites can be detected in urine for up to 12 days. (Pertwee, 2008, Sulak, 2021; TMCI, n.d.)

Inhalation, on the other hand, avoids first pass metabolism so peaks in 1-3 minutes, causing 1-2 times higher peak serum concentrations than oromucosal, which is why adverse effects are much more common with inhalation. As well, the peak effects from inhalation decrease rapidly in 30 minutes lasting a total of 1-3 hours, which is why inhalation is only recommended in medical use for rapid relief of acute symptoms like with panic attacks.

**Side Effects**

Medical cannabis can produce varying side effects and are within the range tolerated for other medication with the most common side effects being dizziness, dry mouth, sleepiness, euphoria, and, with higher doses, disorientation, impaired balance and short-term memory, dysphoria, anxiety, confusion, paranoia, nausea, and vomiting (Whiting et al., 2015). A review of 23 RCTs found there was no higher incidence of serious adverse events in medical cannabis users compared with control, but there was a higher incidence of non-serious side effects with dizziness being the most common and dry mouth the next (Wang et al., 2008).

**Impacts on Side Effects**

Clinical experience has shown that many of the adverse effects can be avoided with the proper dosing and chemovar and are most often due to doses being too high, common with THC over 5-10 mg and CBD over 50-100 mg (Pertwee, 2008; TMCI, n.d.; Sulak, 2021). Cannabis clinicians caution patients against building tolerance which increase their risk for side effects.
since patients start increasing their doses. Tolerance occurs when continued stimulation of cannabinoid receptors leads to saturation, desensitization, and down-regulation, more common with use of higher THC ratios as studies show 15% lower CB1 receptor availability in men using THC regularly (Sulak, 2021). Patients can actively avoid tolerance by abstaining from cannabis for 1-2 days to allow receptors to re-sensitize and up-regulate and can often restart at 50-60% reduced doses. The other less common causes of side effects are due to delivery, most particularly inhalation which causes the highest peak serum concentration and chemovar, most particularly when the ratio is too high in THC which increases side effects and too low in CBD which can mitigate the effects (Sulak, 2021). Dr. Sulak’s Healer site offers excellent videos to help patients find their proper dose and chemovar, avoid side effects and tolerance, and resensitize receptors (Sulak, 2019).

**Biphasic Dose-Response and Bidirectional Effects**

Many notable adverse effects reported such as anxiety, nausea, vomiting, and dysphoria are the very symptoms well-known to be relieved by cannabis. This bidirectional phenomenon is related to the homeostatic function of the ECS and its retrograde signaling which allows the ECS the capacity to influence physiology in opposite directions in order to maintain cellular balance (Pertwee et al., 2008; Sulak, 2021). The other factor contributing to this bidirectional phenomenon is the biphasic dose-response effect of cannabis -- where at first increased doses cause increased effects, like other mono-phasic medications. Beyond a certain threshold dose, the receptors become saturated and start to down-regulate and increasing the doses will instead lead to decreased positive effects while worsening the side effects (Russo et al., 2018; Sulak, 2021). Recent research on cannabis hyperemesis syndrome (CHS) demonstrates this biphasic dose-response effect. Although cannabis is used to relieve nausea and vomiting, long-term
heavy use or for those with genetic mutations that decrease the breakdown of cannabis can actually cause intractable nausea and vomiting that can only be resolved by cessation of cannabis use for weeks or months. (DeVuono et al., 2020; Russo et al., 2021).

**Proper Dosing**

Clinical experience demonstrates this biphasic dose-response can be mitigated with proper dosing and dosing strategies to ensure patients do not go beyond their threshold dose or build tolerance (Sulak, 2021). Cannabis clinicians always advise patients to find their proper dose by “Starting Low” at the lowest doses (1-2 mg) and “Going Slow” only titrating up every 3-5 days to give receptors time to adjust and to fully feel the effects (Sulak, 2021). Clinical trials on Nabiximols revealed the importance of finding the right dose as earlier trials with Nabiximols yielded significant higher rates of adverse effects prior to adopting this slower and lower dose titration schedule (Barnes et al., 2006; Sulak, 2021). Cannabis clinicians also educate their patients about the biphasic dose-response of cannabis, explaining that if they start to notice side effects, then they are probably beyond their threshold dose and need to decrease the dose; but if they start to notice loss of effects, that it is usually a sign their ECS has been overstimulated and tolerance is being built. At this point, clinicians recommend patients abstain completely for a day or two to resensitize and upregulate receptors. (Sulak, 2020; Sulak, 2021; Russo et al, 2021)

**Summary of Cannabis Pharmacology**

In summary, it is important to understand that cannabis does not adhere to the same set of pharmacology rules as other medications due to the retrograde signaling of the ECS and capacity to produce bidirectional effects. Providers need to be aware that most of the adverse effects from cannabis can easily be avoided by using the proper dose, dosing strategies, chemovar, delivery and by avoiding building tolerance.
CHAPTER 6

STRATEGIES TO MINIMIZE HARM AND MAXIMIZE BENEFIT

Providers need to be made aware of the following strategies discussed above and summarized below that can minimize harm and maximize benefit for patients using medical cannabis:

- **DO NOT SMOKE CANNABIS.** Inhalation should be with flower vaporizer only and only for rapid relief of acute symptoms.

- **CHOOSE WHOLE PLANT CANNABIS** products that are LABORATORY TESTED, ideally with third party testing to know the exact contents of medicine.

- **CBD IS NON-INTOXICATING.** There is conclusive evidence CBD is safe and effective for treating inflammation, mental health conditions, addiction, seizures, mitigating side effects from THC, hepatic illness, pain, nausea, and vomiting, without side effects. For those more vulnerable to impairments such as the elderly and adolescent population, consider CBD-rich cannabis first.

- **THC CAN BE INTOXICATING.** THC is most effective for pain, sleep, spasms, nausea, and vomiting but can be intoxicating and has significant dose-dependent side effects, especially in doses greater than 5-10 mg which can temporarily increase heart rate, anxiety, sedation, and impair memory and balance.

- **CAUTION IF USING THC** in the following conditions:
  
  o Unstable heart disease or use of heart medications (risk: MI)

  o Severe psychiatric illness (risk: worsening of bipolar symptoms or earlier onset schizophrenia for those predisposed)

  o Hepatic illness with active inflammation and scarring (risk: increased fibrosis)
• Elderly (risk: falls due to dizziness and impaired motor coordination)
• History of substance-abuse (risk: CUD, especially with inhalation)
• Pregnant/Lactating (risk with inhalation and heavy use: dysregulation of ECS)
• Immunocompromised (risk with inhalation: lung infection if contaminated product).

- CHECK FOR DRUG-DRUG INTERACTIONS on Medscape or drugs.com.
- FIND THE RIGHT DOSE, critical to maximize benefits and minimize side effects.
  • START LOW, (i.e., 1-5 mg for CBD, 1 mg for THC) and assess for effects.
  • GO SLOW, titrate up every 3-5 days if needed.
  • IF SIDE EFFECTS, decrease dose.
  • IF LOSS OF EFFECTS/TOLERANCE, abstain for 1-2 days to resensitize receptors.

- USE OROMUCOSAL delivery for longer duration and measured and controlled dosing.
- AVOID TOLERANCE AND HEAVY USE (risk: CUD and increased side effects).
- AVOID DRIVING or operating machinery until response to strain/dosage determined.
- STORE MEDICAL CANNABIS in child-proof container.
- COMMUNICATE with medical providers for guidance on proper dose and ratio of THC:CBD as evidence-based research is emerging rapidly. (Sulak, 2021)
CHAPTER 7

CLINICAL EVIDENCE ON MEDICAL CANNABIS

There is a considerable amount of research on the clinical evidence of medical cannabis of various conditions, but the two most comprehensive reports are those from the World Health Organization and the National Academies of Sciences, Engineering, and Medicine (NASEM), the latter one what the educational presentation was mostly focused on, updated with recent research as appropriate (Madras, 2015; NASEM, 2017).

NASEM Report

After reviewing more than 10,000 studies, the NASEM committee reached nearly 100 conclusions, which supported the medical utility of cannabis and determined that the medical conditions patients used medical cannabis for had strong evidence 86% of the time (NASEM, 2017; Rapaport, 2017).

Due to the political restrictions on research discussed earlier, the committee concedes their results are generalized and limited by the scope of this research and lack of differentiation between medical use and recreational use (NASEM, 2017). The report also is limited by the studies that were available at the time, which were mostly focused on spasticity, nausea and vomiting, anorexia, and chronic pain, and therefore do not address many of the qualifying conditions patients use cannabis to treat (NCSBN, 2018).

The report also lacks information critical for providers caring for patients in clinical practice, such as dosage, method of administration, duration, frequency, chemovar/ratio of THC:CBD, drug interactions, etc. There are some conclusions for which the committee was able to distinguish the kind of cannabis or method used and included these distinctions in parentheses.
when available. Despite the limitations in specificity and for conditions, the committee’s conclusions on the evidence at the time offers valuable insight into the medical use of cannabis.

**Definitions of Evidence**

Before reviewing the conclusions, it is important to understand the terminology provided by the committee to clarify the level of evidence concluded. The level of evidence is ranked from conclusive, substantial, moderate, limited, to insufficient with ‘conclusive’ being strong evidence from RCTs that support cannabis as an effective or ineffective treatment with many supportive findings from good-quality studies and no credible opposing finds or evidence of chance, bias, and confounding factors, meaning a firm conclusion can be made. ‘Substantial’ is similar to conclusive but with minor limitations including chance, bias, and confounding factors that cannot be ruled out. ‘Moderate’ has some evidence with several findings from good- to fair-quality studies but chance, bias, and confounding factors cannot be ruled out, while ‘limited’ means there is weak evidence from fair-quality studies and conclusions can be made but with significant uncertainty due to chance, bias, or confounding factors. ‘Insufficient’ means there is not enough evidence to support that cannabis is either an effective or ineffective treatment due to mixed findings or single poor studies with significant uncertainty due to chance, bias, and confounding factors (NASEM, 2017).

**Safety Profile of Medical Cannabis**

**Non-Lethal, Non-Toxic**

The committee’s conclusions regarding the safety of cannabis determined that cannabis is non-lethal and non-toxic with “no evidence of any deaths due to cannabis use or overdose” (NASEM, 2017). This is supported by extensive research on the pharmacology of cannabis revealing that there are no cannabinoid receptors on the cardiorespiratory receptors meaning
cannabis cannot stop breathing or heart rate, unlike opioids can (Glass et al., 1997; Grotenhermen, 2004; Russo & Marco, 2017; Sulak, 2020). Other research in animal studies, one giving monkeys 9000 mg/kg of THC, over 180 times the maximum human amount, has “failed to find a lethal acute dosage of cannabis, and have found that the doses of long-term cannabis required to produce toxicity and death in animals were so high it would be nearly impossible for a human to consume such quantities via ingestion or inhalation” (Joy et al., 1999; Sulak, 2020; Thompson et al., 1974). Providers may be more confident discussing and recommending medical cannabis when they realize that there is conclusive evidence that cannabis is safe, non-lethal, and non-toxic with no evidence of death or overdose.

Not a Gate-Way Drug

Regarding cannabis being a gate-way drug, the committee found ‘limited evidence’ that cannabis “led to tobacco use or other illicit substances,” or “increased the risk of addiction” (NASEM, 2017). This is supported by current research showing that CBD has anti-addictive effects that can help treat disorders of addiction including tobacco use, recently confirmed by RCTs using CBD for opioid use disorder (Hurd et al., 2019; Nahler et al., 2019; Prud’homme et al., 2015). It may help providers counter the stigma of cannabis to know there is limited evidence that cannabis is a gate-way drug or increases addiction risk, and this was a myth started by Aslinger’s campaign to criminalize cannabis, which he later admitted in emails was fabricated, that has unfortunately been propagated throughout the years (Bearman, 2017; Earleywine, 2005; Wing, 2014).

Low Risk for CUD with Medical Use

As for the question of cannabis having a high risk of abuse, known as cannabis use disorder (CUD), the committee found an association with CUD and the use of higher THC and
certain risk factors. They found there was ‘substantial evidence’ for the ‘risk of problem cannabis use’ in those who are male and smoke cigarettes, and ‘moderate evidence’ for those who are frequent heavy users, have combined use of nicotine and abused drugs, have childhood sexual abuse and parental substance use, poor school performance, antisocial behaviors, and initiate cannabis at an earlier age (NASEM, 2017). However, the committee did not differentiate between medical use and recreational use which recent research clarifies does differ in the risk for abuse.

Long-term studies of patients in the UK, Germany, and Switzerland using Nabiximols (1:1 THC:CBD) for multiple sclerosis showed no sign of abuse, dependence, or diversion in 30,000 patient-years of recorded usage (Russo et al., 2015). This is most likely due to the inclusion of CBD which has an established low risk for addiction as CBD does not produce euphoria or stimulate the reward center in the brain and can block THC’s ability to do this -- many studies have used CBD to successfully reduce addiction and cravings in many disorders including tobacco, alcohol, and opioid use (Hurd et al., 2019; Prud’homme et al., 2015; Russo & Marco, 2017; Sulak, 2021). Studies analyzing the impact of medical cannabis legalization on CUD compared to recreational legalization found that medical cannabis legalization has not increased the risk of abuse and that the increased risk of abuse is only associated with recreational legalization and use of higher THC cannabis, which unlike CBD, does stimulate the reward centers in the brain, especially with inhalation which increases the peak serum concentration in the brain (Cerda, 2020; Sulak, 2021; Williams, 2017).

**Low Risk for Dependence**

To put this risk of abuse in perspective, research has found that 4% of those who use cannabis meet criteria for CUD, with the addictive potential of cannabis (i.e., cravings or use
despite problems from use) similar to caffeine, usually occurring with heavy and prolonged use (Anthony, 2001; Joy et al., 1999; Russo et al., 2015; Sulak, 2021). As for the risk of dependence with recreational cannabis use (i.e., withdrawal symptoms with cessation), it is estimated to be 9%, compared to alcohol at 15% and nicotine at 32% (Anthony et al., 1997; Lopez-Quintero et al., 2011; Patel & Marwaha, 2021). A risk of dependence with cannabis use exists, but it is mild and almost two times lower than alcohol and almost four times lower than nicotine. The withdrawal symptoms from cannabis are also comparable to caffeine (i.e., irritability, restlessness, sleep disturbances due to strange dreams, decreased appetite) and are usually mild due to the long half-life of cannabis (t½ 1-2 days) and occur one to two days after abrupt cessation, peak in two to five days, and resolve in one to two weeks (D’Souza et al., 2016; Grotenhermen, 2003; Huestis, 2007; Sulak, 2020).

Increased Risk for Injuries with Driving and Accidental Ingestion

The committee did find “substantial evidence” that cannabis use “increased risk for driving accidents (MVA)” and “increased risk of overdose injuries due to accidental ingestion in children.” Since CBD is non-impairing, these risks are only associated with the use of higher THC cannabis. Some meta-analyses of the risk of MVA with cannabis are inconclusive, with some showing no risk of MVA and others showing increased risk of low-moderate magnitude with an odds-ratio (OR) of 1.36, compared with the risk of texting OR of 2.22, which is likely due to the dose, route, ratio to CBD, and patient tolerance, all critical factors influencing impairment (Hostiuc, 2018). There is no standard breath, urine, or blood test to determine intoxication because of these confounding factors, but roadside sobriety tests can be used to measure impairment (Armentano, 2013). Countries who have legalized recreational use like Canada have countered this risk by granting law enforcement more authority to conduct impaired
driving tests based not on drug level but functional impairment (Williams, 2018). Providers need to be aware of the increased risk for MVA with cannabis use and instruct patients not to drive or operate heavy machinery until they know their response to the chemovar and dosage, cautioning patients that THC can impair motor coordination and concentration, especially in new users, dose increases, and with inhalation that increases serum peak concentration (Sulak, 2020).

**Uncertain Risk for Prenatal, Perinatal, Neonatal Exposure**

In regard to prenatal, perinatal, and neonatal exposure to cannabis, there was ‘insufficient evidence’ to make conclusions in regard to pregnancy and child outcomes since the studies linking cannabis to premature birth or childhood leukemia were low quality and did not control for confounders. There was ‘substantial evidence’ that smoking cannabis during pregnancy is linked to lower birth weight in the offspring (NASEM, 2017). Although smoking cannabis is not recommended in medical use, it is still important to assess the effects of cannabis itself in pregnancy, especially considering that approximately 1 in 25 women use cannabis during pregnancy (Alshaarawy & Anthony, 2019.)

Most of the studies on pregnancy at the time of the NASEM report were limited to observational data and did not control for alcohol or tobacco use making it difficult to accurately assess risks. A recent meta-analysis that did control for smoking exposure found there was no association between cannabis use in pregnancy and lower birthweight, confirmed by two other recent studies (Connor et al., 2018; Ko et al., 2018; Sturrock et al., 2020). Recent research on effects for offspring have found that cannabis is not teratogenic, but that THC does cross into the placenta and is excreted into breast milk, up to 2.5% of THC per kg of weight of maternal dose with inhalation (Baker et al., 2018). For example, if a pregnant woman weighs 60 kg and smokes 30 mg of THC (0.5 mg/kg), her 5 kg fetus might be exposed to 0.0125 mg of THC.
Although this level seems insignificant, especially considering levels of natural 2-AG in breast milk are found to be 119-431 ng/mL, it is possible that heavy use of THC could downregulate or disrupt ECS signaling that is critical in developing brain (Bertrand et al., 2018; Gaitan et al., 2018; Grant et al., 2018; Sulak 2021).

The American Academy of Pediatrics advises avoiding cannabis during pregnancy and lactation but does not recommend stopping or discarding milk as the benefits of breast-feeding are so clear and the risks of phytocannabinoids so uncertain (Ryan et al., 2021). Most cannabis clinicians follow the AAP guidance of not recommending cannabis in pregnancy and lactation, and only support medical cannabis use (i.e., lowest dose, ratios higher in CBD, oral delivery only) when the benefits clearly outweigh the risks, such as with hyperemesis gravidarum, chronic pain, and PTSD -- conditions that cause high levels of maternal stress and require teratogenic medications to treat, but respond well to low-dose medical cannabis (Sulak, 2021).

Summary of Safety Profile

To summarize the safety concerns of cannabis, providers need to be aware that cannabis is very safe. It is non-fatal, non-toxic, not a gate-way drug, and not addictive. Instead, providers should caution patients that there is a 4% risk of CUD and 9% risk of dependence in patients using THC long-term, with increased risk in those who use inhalation, are male, smoke cigarettes, started at an earlier age, and have a history of substance abuse or psychiatric conditions. Providers should also be instructing patients not to drive while impaired, to always keep their medical cannabis in child-proof containers, and to avoid use in pregnancy and lactation without first consulting their provider.
**Adverse Effects: Cardiovascular, Pulmonary, and Psychological**

Regarding the risk of adverse effects, the committee found no evidence of risk for organ damage but did find evidence, expanded upon by current research, of adverse effects increased in certain conditions for primarily three systems: cardiovascular, pulmonary, and psychological (NASEM, 2017; TMCI, n.d.).

The cardiovascular adverse effects from cannabis are associated with inhalation of THC in those with cardiovascular disease. It is well established that cannabis can temporarily increase heart rate and decrease blood pressure which for most patients is mild and tolerable, but, in those with severely unstable heart disease who cannot handle the increased load, these effects could be harmful and increase the risk of myocardial infarction (Naliboff et al., 1976; Russo, 2015; Sulak, 2020). However, a recent systematic review of non-clinical studies has shown that CBD can have cardioprotective effects protecting the heart from damage of heart attacks with one study showing that very-low doses of THC may also be cardioprotective (Shayesteh et al., 2019; Waldman et al., 2013).

The pulmonary adverse effects of cannabis are associated with smoking which is not recommended in medical use as there is substantial evidence that smoking cannabis worsens respiratory symptoms - increasing cough, sputum production, and risk for upper respiratory infections - but does not increase shortness of breath or the risk of lung cancer (NASEM, 2017). Smoke is well known for containing toxins and carcinogens which can damage airways and is not recommended as a delivery method in medical use, but cannabis itself is found to have bronchodilatory and anticarcinogenic effects (Sulak, 2021; Whiting et al., 2015). The respiratory effects from smoking cannabis were found to be temporary, improving after quitting smoking, with no risk of chronic bronchitis compared to nonsmokers at 10 year follow up (Tashkin, 2013).
After controlling for tobacco exposure, several large data sets on heavy cannabis smokers do not show evidence of COPD even after 20 joint-years or increased rates of upper and lower respiratory cancers compared to those who do not smoke cannabis which is thought to be due to the anti-inflammatory and anti-carcinogenic effects of cannabinoids counteracting the toxins (Hashibe et al., 2006; Whiting et al., 2015; Sulak, 2021).

Regardless, smoking cannabis is still not recommended as there have been several cases of spontaneous pneumothorax and some cases of pulmonary aspergillosis in immunocompromised patients from smoking contaminated cannabis. The other significant concern with inhalation of cannabis is E-cigarette or vaping product use-associated lung injury (EVALI) which is thought to be due to diluents in vaping cartridges, especially Vitamin E acetate (Dinakar & O’Connor, 2016; Raber et al., 2015; Ryan et al., 2021). As of Feb 2020, there were 2,807 cases of EVALI hospitalizations in America and 68 deaths, with 82% involving THC-containing products (Sulak, 2021). Although these are associated with the use of Vitamin E acetate, there are other harmful compounds that have been found in these vaping concentrates such as butane, pesticides, metals, and the flavorings with propylene glycol or glycerol which increase the risk of formaldehyde production and carcinogenic risks (Dinekar & O’Connor; Raber et al., 2015; Sulak, 2021).

Due to these concerns, it is critical that providers instruct patients not to smoke cannabis or vape cartridges, and if they need rapid relief from acute symptoms, then they should only inhale from a flower vaporizer that vaporizes flowers, preferably third-party tested to ensure no contaminants (Sulak, 2020; Sulak, 2021).

The final concern for adverse effects found by the committee and further clarified by recent research is the psychological effects of cannabis. The committee found many results,
sometimes seemingly contradictory, but concluded there was: ‘substantial evidence’ that frequent use of THC increases the risk of earlier onset of schizophrenia in those predisposed, but ‘moderate evidence’ of ‘better cognitive performance for those with psychotic disorders’; and ‘moderate evidence’ that heavy cannabis use can increase symptoms for those with bipolar disorder and increase suicidal ideation, though some studies showed improved symptoms with cannabis use; ‘moderate evidence’ that THC can temporarily impair learning and memory, but ‘limited evidence’ of long-term impairment to academic achievement or social functioning, and in some studies using CBD improved focus and concentration (NASEM, 2017). The next section on the impact of dose and ratio on the psychological effects with medical cannabis use will help to elucidate these seemingly contradictory findings.

Considerations for Psychological Effects

**Bidirectional Effects.** The concept of bidirectional effects and biphasic dose-response is a major contributing factor in many of the psychological adverse effects from cannabis. For example, anxiety has been found to be relieved with proper doses and ratios with lower THC, but higher doses of THC have been found to exacerbate anxiety, even to the point of paranoia and panic attacks (Russo et al., 2015). Due to the high number of cannabinoid receptors in the brain, it is not surprising that there are several potential acute central nervous system effects with cannabis use. Some of these can be positive (anxiolytic and anti-psychotic effects associated mostly with CBD), and some negative (impaired short-term memory and anxiogenesis, associated with higher levels of THC (Russo et al., 2015). The negative psychological effects can usually be avoided with the proper dosing and ratio as is done in medical use and discussed above.

**Lower Risk with Medical Use.** Recent research investigating the effects of cannabis on psychological or cognitive disorders supports the benefits of medical use compared to
A 2017 comprehensive systematic review evaluated studies of medical cannabis for outcomes related to anxiety, depression, and neurocognition. The first conclusion was that mental health is a prominent reason for seeking medical cannabis, however, there is far less literature on medical use of cannabis and mental health outcomes compared to that of nonmedical use (Walsh et al., 2017). The other conclusions were as follows: all of the 8 cross-sectional studies reported anxiolysis; 7 out of 9 studies on depressed mood noted improvement in depression and pain; preliminary evidence shows potential for treating PTSD and addiction; one study showed a positive association between depression severity and CUD; and the use of medical cannabis does not increase harm to self or others (Walsh et al., 2017).

Long-term data on adverse effects from medical use of Nabiximols trials collected by observational registry on 941 pts with 2,214 patient-years of exposure showed 6% of the patients experienced psychiatric adverse effects (depressed mood, anxiety), with 2% having suicidal ideation, but no evidence of abuse, dependence, or long-term cognitive impairment (Etges et al., 2016).

**Benefits May Outweigh Risks.** Though these risks are low, they still must be considered in those with mental health issues more vulnerable to the risk of mood dysregulation. However, recent studies on medical use show the benefits of using cannabis for mental health issues may outweigh these risks, especially considering that traditional medications for mental health are not very effective and have adverse effects leading to noncompliance (Pinto et al., 2020). The first neuroimaging study of twenty-two patients using medical cannabis (for pain, anxiety, PTSD, sleep) showed their brain activity normalized after three months of treatment with medical cannabis, looking similar to healthy controls, and also noted reported improvements in task
performance, impulse control, sleep, quality of life, and a decrease in use of conventional medications including opioids (Gruber et al., 2018)

The studies using CBD for mental health issues show high efficacy as well, with a recent systematic review on CBD showing there is promising evidence on CBD’s potential to be a novel treatment for mood disorders as they have a different mechanism of action than the less effective conventional antidepressant medications which only target monoaminergic pathways (Linge et al., 2016; Pinto et al., 2020). This was confirmed by another 2020 systematic review saying CBD and Nabiximols were helpful in alleviating symptoms of cannabis-related disorders, schizophrenia, social anxiety disorder, and comorbidities of autism and attention deficit disorder with moderate recommendation (Khan et al., 2020). Preclinical evidence shows the potential of CBD to reduce anxiety in PTSD, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and seasonal affective disorder, with clinical trials finding 300-600 mg CBD effectively reduced anxiety (Blessing et al., 2015). A recent case series on anxiety found CBD doses ranging from 25-275 mg reduced daily anxiety scores for 79% of the patients, with most finding improvement at only 25 mg (Elms et al., 2019).

**Caution with Bipolar Disorder and THC:** Research on THC shows that low dose THC (less than 7.5 mg) may have anxiolytic effects, but higher doses (12.5 mg and over) increase anxiety, and more sensitive patients may feel anxiety even at doses over 5 mg (Cuttler et al., 2018). This emphasizes the importance of selecting the right ratio and dose and gives insight into contradictory findings that nonmedical use of cannabis may exacerbate bipolar symptoms, but other times is relieved by it (NASEM, 2017; Walsh et al., 2017).

A 2020 systematic review concluded that CBD shows potential to relieve symptoms of bipolar disorder, however, more research is needed before recommending CBD as a treatment,
especially considering the bidirectional effects of CBD where lower doses are alerting but higher can be sedating (Pinto et al., 2020). As well, the risk may not be worth the benefit considering there was quality evidence showing heavy use cannabis can increase symptoms of mania and risk for new onset symptoms up to three-fold (Gibbs et al., 2015). In summary, providers should be aware that caution is warranted for patients with bipolar disorder using medical cannabis and best avoided until further research and clarification.

**Caution with Schizophrenia and THC.** The current research on schizophrenia clarifies that cannabis use is associated with, but not causative, of the earlier onset but only in patients with heavy use and high dose THC and who are genetically predisposed (Frisher et al., 2009; Hickman et al., 2009; Ksir & Hart, 2016). The research also found the incidence to be very low: 1 case in 2,800 heavy cannabis users ages 20-24 (the highest risk group), and 1 case in 10,000 light cannabis users in the same age group (Ksir & Hart, 2016). Furthermore, recent research has shown CBD can be very effective in treating the symptoms of schizophrenia: one RCT showed 1000 mg/d CBD improved symptoms of schizophrenia in 79% of patients using over 6 weeks, and other RCTs showed 200-800 mg/d CBD was more effective than amisulpride at reducing symptom severity with fewer extrapyramidal side effects (Gururajan & Malone, 2016; Leweke, Mueller, Lange, & Rohleder, 2016; McGuire et al., 2018). Again, this highlights how careful selection of dose and ratio are key to avoiding bidirectional effects with cannabis, especially in those with more severe mental health issues.

**Caution with Cognition and THC:** Research investigating the cognitive impairment with medical cannabis also shows that the impairment is not associated with medical use and is not long-term. However, the use of high dose THC can impair recall for sometimes weeks, especially in adolescents. An eight-year study of 2,404 patients using cannabis showed no long-
term impact to cognitive function in all domains except for recall which did return to baseline but after a month of cessation (Tait et al., 2011). A recent review of RCTs showed THC can cause mild residual cognitive effects (i.e., working memory, processing speed, and executive functions) and can last days to weeks for some adults, longer in adolescents and longer with use of higher doses (Bourque & Potvin, 2021). However, studies on the impact of ratios higher in CBD showed CBD had protective effects against the cognitive impairments of THC and can also improve focus and concentration (Colizzi & Bhattacharyya, 2017; Kahn et al., 2020). Providers need to be aware that medical cannabis does not cause permanent cognitive impairment in adults, but heavy use of THC can have residual effects on short-term memory that could last weeks, especially in adolescents and those using higher doses of THC. However, providers should also be aware that CBD can protect against these effects and improve focus and concentration, again emphasizing the importance of dose and ratio selection, especially in adolescents.

**Recommendations for Doses/Ratios:** In summary, providers should be aware that more research is urgently needed on the use of medical cannabis for mental health issues but that current research demonstrates its potential to improve symptoms especially for anxiety and mood disorders and especially with moderate-high doses of CBD (25-600 mg). Providers should also be aware that patients with a personal history of bipolar disorder should avoid heavy use and high dose THC due to the risk of exacerbation of bipolar symptoms, and though CBD may have potential to reduce bipolar symptoms more research is needed before recommending. Providers should also be aware that patients with a family history of schizophrenia have an associated risk of earlier onset with heavy use and high dose THC but may find relief with high dose CBD. As for the risks of cognitive impairment, providers should caution patients that THC can impair short-term memory which can last several weeks in adolescents and those using higher doses and
ratios of THC, but ratios with higher CBD can protect against this impairment and improve focus and concentration.

**Efficacy of Cannabis for Various Conditions**

The NASEM report concluded there was evidence for the efficacy of cannabis for treating many medical conditions with various levels of evidence listed below and the type of cannabis listed in parenthesis when available.

**Conclusive and Substantial Evidence Effective For:**

- Chronic pain (cannabis)
- Antiemetic for chemotherapy-induced nausea and vomiting (oral cannabinoids)
- Spasticity from MS or spinal cord injury (oral cannabinoids)

**Moderate Evidence Effective For:**

- Improving sleep for those with OSA, fibromyalgia, chronic pain, and MS (cannabinoids, Nabiximols)

**Limited Evidence Effective For:**

- Increasing appetite and decreasing weight loss associated with HIV/AIDS
- Improving clinician-measured MS spasticity symptoms (oral cannabinoids)
- Tourette Syndrome (THC capsules)
- Anxiety symptoms for social anxiety disorders (CBD)
- PTSD (nabilone – THC)
- TBI + intra-cranial hemorrhage (cannabinoids)

**Limited Evidence Ineffective For:**

- Dementia, IOP, and Depression
Summary for Efficacy of Medical Cannabis

The NASEM report acknowledged the medical utility of cannabis and concluded that it was safe and effective for many conditions, most notably for treating chronic pain, nausea and vomiting, spasticity, and sleep disturbances. The report also acknowledged the limitations to research due to Schedule I status that resulted in ‘insufficient evidence’ at the time to support or refute the efficacy of cannabis for treating many conditions patients use it for: cancer-associated anorexia/cachexia, IBS symptoms, epilepsy, spasticity in paralysis due to spinal cord injury, ALS symptoms, chorea and symptoms from Huntington’s disease, Parkinson’s motor symptoms, abstinence of addictive substances, schizophrenia (NASEM, 2017). The committee acknowledged the need for further research and therefore recommended that cannabis be rescheduled to allow for this (NASEM, 2017).
CHAPTER 8
THE CURRENT RESEARCH ON MEDICAL CANNABIS

Since the publication of the NASEM report, additional evidence has been collected and current clinical research has established the efficacy of using cannabis to treat several of the conditions that the NASEM report found to only have limited or insufficient evidence at the time, most notably for neurological conditions refractory to conventional treatment: epilepsy, spasticity, neuropathic pain, insomnia, and addiction (Russo et al., 2018; Sulak, 2021).

Since 2018, clinical trials have been determining the efficacy of cannabis for treating epilepsy (Phase III - CBD, FDA approved in 2018 as Epidiolex); multiple sclerosis spasticity (Phase III - Nabiximols, awaiting FDA approval as Sativex in 2021); chronic pain (Phase II - THC, Nabiximols), schizophrenia (Phase II - CBD), sleep disturbance (Phase II-III THC, nabilone, Nabiximols), glaucoma (Phase II - THC), Tourette syndrome (Phase II- THC), and social anxiety (Phase II- BCD) (Russo et al., 2018). There is also promising clinical research for the use of medical cannabis with opioid addiction (i.e., CBD during the day and THC at night for sleep or pain), anxiety and mood disorders (CBD), dementia w/ agitation (low-dose THC), Parkinson’s Disease (CBD, THC), and PTSD (cannabis) (Sulak, 2021; Russo et al., 2018).

Providers should be aware that the NASEM report provides a comprehensive review of scientific literature up to 2017 but is outdated now by current research adding to the evidence daily making it critical to stay abreast of new information and maintain open lines of communication with patients (TMCI, n.d.).

**Resources for Research**

The current research for some of the conditions such as anxiety, mood disorders and schizophrenia were discussed prior while others are briefly summarized below. But more in-
depth information on all these conditions can be found in the resources mentioned earlier such as Dr. Sulak’s book and the TMCI and SCC websites. As providers review the research below, it is important to keep in mind that the most challenging factor for patients using medical cannabis is figuring out HOW to use it -- what dose, ratio, duration, delivery is most effective for treating their condition or symptoms. A new software program called CannaKeys was recently developed to address this need and features up to date meta-analyses of the latest research for nearly 240 conditions and offers insight into clinical dosing summaries and chemotype guidance (CannaKeys, 2021). Cannabis clinicians that have been working with patients for years are also a valuable resource that can offer much-needed guidance here. Though much more research is needed to have evidence-based protocols to properly guide patients, it is important to remember that some guidance from high quality research and resources is a better alternative to none.

**Neuropathic Pain**

Chronic pain is the number one reason why patients seek medical cannabis and with conclusive evidence to support its use (NASEM, 2017). A recent Reuters study analyzing state registry data that tracks the conditions for which patients use cannabis found 65% of medical cannabis patients seek cannabis for chronic pain (Rapaport, 2019). A 2021 study offers insight into which ratios may work best for neuropathic pain, one of the most difficult to treat with conventional treatment. Using a multicriteria decision analysis, the study compared pharmacotherapy for chronic neuropathic pain, including cannabis, scoring the drugs on seventeen effect criteria relative to benefits and safety. The results demonstrated that cannabis was more effective for chronic neuropathic pain than duloxetine, gabapentin, SSRIs and opioids, with the most effective ratio being 1:1 THC:CBD (scoring 79 out of 100), followed by CBD-
dominant (75), then THC dominant (72), with duloxetine and gabapentoids (60’s), amitriptyline, tramadol and ibuprofen (50’s), morphine and fentanyl (30’s) all less effective (Nutt et al., 2021).

**Insomnia**

Insomnia is the second most common condition for using medical cannabis and many patients report improvement in sleep with a variety of chemovars most notably THC-rich cannabis, but also combinations of THC and CBD-rich, THC and CBN-rich (CBN is known as cannabinol which can cause drowsiness), and those with terpene content higher in myrcene, known to be sedating (Kesner & Lovinger, 2020). However, finding the right chemovar and the right dose is essential to having sedation without the impairment from THC. For example, research using THC with 1-2 mg CBD found CBD could mitigate the memory-impairing effects of THC but using CBD doses as small as 5-15 mg was found to interfere with stage 3 sleep (Nicholson et al., 2004). A recent RCT with 23 patients showed promising results using a cannabinoid formulation with 10 mg THC/1mg CBD and 0.5 mg CBN, 0.5 mL sublingual administered one hour to desired sleep time for two weeks. This combination proved to be very effective for improving sleep and sleep quality and was well-tolerated with the most common adverse effects being dizziness and dry mouth (Walsh et al., 2021).

**Epilepsy**

In 2015, a CNN documentary ‘Weed’ publicized the remarkable experience of 7-year-old Charlotte Figi, who used a whole plant extract high in CBD (1:30, 0.5% THC and 17% CBD) which reduced her seizures from 40 a day to 2-4 a month (CNN: Weed, 2015). This led many families desperate for hope to turn to CBD to treat their child’s epilepsy and eventually led to the development of Epidiolex (Nahler, Jones, & Russo, 2019). Though the NASEM report did not have enough evidence at the time regarding the efficacy of cannabis to treat seizures, later
clinical trials using the purified CBD ‘Epidiolex’ revealed it was safe, effective, and in 2018 led to the FDA-approval in the United States and eventual de-scheduling of all CBD products (Devinsky et al., 2017; Healthcare professionals [GW], n.d.; Ryan et al., 2021).

A 2018 meta-analysis comparing Epidiolex to whole-plant CBD found whole-plant CBD had even superior efficacy with approximately 25% of patients using Epidiolex (~27 mg/kg/d) having over 50% reduction in seizures, while 55% patients using CBD-rich cannabis (~6 mg/kg/d) had over 50% reduction in seizures with lower doses and less side effects (Pamplona et al., 2018). Other trials using the more effective whole-plant cannabis have found that treating seizures with cannabis can be very complex, but when proper doses and ratios are found can profoundly reduce seizures and improve quality of life (QOL), particularly mood, behaviors, and communication (Rosenbert et al., 2017).

Research has found that CBD-dominant oil works best with a small amount of THC to reduce excitotoxicity in the brain (1:20-30) and has a wide dosing range (0.05 – 25 mg/kg/d) but is often effective at lower doses. Trials using CBD-dominant oil found 86% of 272 patients that had previously failed to respond to anti-epileptic drugs (AEDs) reported benefits, 10% became seizure-free, 45% reduced seizures by 50%, 14% had no reduction, and 4% had worsening of seizures (Sulak et al., 2017). This risk is small but should be noted that in the wrong patient and wrong dose, seizures can increase. Other research using CBD as an adjuvant AEDS found there were drug-drug interactions (most notably with clobazam where levels were increased by CBD up to 3-8 times) where levels of AEDs could be raised or lowered depending on which enzymes they were metabolized by and if CBD inhibited or induced metabolism (Chen et al., 2019; Devinsky et al., 2018).
Providers should be aware that CBD can be quite effective at reducing seizures and improving QOL with no toxicity and much fewer side effects than AEDs when the right dose is found. However, 4% of patients may see an increase in seizures, and those using CBD in conjunction with AEDs must be closely monitored for drug interactions. Dr. Sulak’s Healer site offers helpful information for parents who want to try using CBD to reduce their child’s seizures: healer.com/pediatric-seizures-video-guide/ (Sulak, 2019).

**Opioid Use Disorder**

Although no drug is strong enough to solve the tragic opioid epidemic or cure a person with opioid dependence, cannabis is showing great promise in reducing cravings, use, and harm, and is a powerful tool that can certainly help (Sulak, 2021). A 2021 report on the impact of medical and recreation marijuana laws on opioid prescribing found states with cannabis laws were associated with 9-27% reduction in MME (morphine mg equivalents), decreased emergency department admissions, and more importantly decreased deaths (Wen et al., 2021). A 2017 systematic review and meta-analysis revealed that cannabis can prevent opioid withdrawal, prevent opioid tolerance, and potentiate opioid analgesia leading to reduced doses (Nielsen, S. et al. 2017). A recent survey on the effect of medical cannabis on prescription opioids for the treatment of chronic pain found cannabis helped ~40% to stop using opioids, ~43% to reduce dose, with many reporting reduced pain (47%), improved function (80%), improved QOL (87%) (Takakuwa & Sulak, 2020).

Typical to many conditions using medical cannabis, the challenge is not finding evidence that cannabis can help but is finding the right dose to increase efficacy and decrease side effects. A 2015 systematic review on animal studies showed that CBD can reduce the intoxication and relapse phase through its action at the 5-HT1 receptors where it reduces the reward-facilitating
effects of morphine but noted that CBD had little effect on withdrawal unless combined with some THC which was effective at reducing withdrawal symptoms (Prud'homme et al, 2015). A 2019 double-blind RCT with 42 drug-abstinent people with heroin use disorder found that CBD 400 mg and 800 mg were both effective at reducing cue-induced craving and anxiety both in the short-term (1-2 hours after and 24 hours after taking the CBD) and at 7 days after the final dose (Hurd et al., 2019). It is noteworthy how quickly CBD worked to reduce cravings and that it lasted 7 days. It is not likely that levels of CBD in the body were significant 7 days later so the effects are most likely due to changes in the brain's pathways related to addiction, craving, and anxiety, demonstrating that the effects of CBD can outlive its presence in the body (Sulak, 2019).

In 2020, a committee of expert cannabis physicians from Canada and the United States came up with consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control (See Figure 8.1 below). Their recommendations include starting with 5-20 mg CBD dominant oral extract, titrating up once or twice weekly as required (with suggestion to add THC 0.5-3 mg for sleep or with pain, which can also increase by 1-2 mg once or twice weekly up to 30-40 mg/day) (Sihota et al., 2020).

When the patient reports a minor/major improvement in function, seeks less as-needed medication to control pain and/or the cannabis dose has been optimized, opioid tapering can be initiated. The opioid tapering schedule may be 5%-10% of the morphine equivalent dose (MED) every 1 to 4 weeks (although some clinicians report patients can do a rapid taper in the first two weeks with 20-50% of MMD) (Sulak, 2021). Clinical success is defined by an improvement in function/quality of life, a ≥30% reduction in pain intensity, a ≥25% reduction in opioid dose, a reduction in opioid dose to <90 mg MED and/or reduction in opioid-related adverse events (Sihota et al., 2020).
Hepatitis C

Many patients with Hepatitis C use cannabis to help with nausea and pain and to endure the side effects from Hepatitis C medications, and research found that those using cannabis concurrently with Hepatitis C IV meds were more likely to complete and respond to treatment. However, the ECS can modulate liver fibrogenesis with bidirectional effects, with CB1 activation promoting fibrosis and CB2 activation inhibiting it, and warrants caution, especially when using THC. A 2008 study on patients with Hepatitis C using high doses of THC was
associated with increased fibrosis in patients with active inflammation and scarring already present (Ishida et al., 2008). However, a later study in 2014 found patients with hepatitis C without active inflammation and scarring had no evidence of increased fibrosis with use of cannabis (Liu et al., 2014).

Research on use of CBD for patients with Hepatitis C shows the potential for CBD to prevent liver scarring and inflammation in hepatitis C (Lim et al., 2011). Preclinical evidence using CBD to treat chronic liver disease shows CBD can reduce steatosis and fibrosis in liver by: reducing lipid accumulation, stimulating autophagy, modulating inflammation, reducing oxidative stress, and inducing death of activated hepatite stellate cells (DeTernay et al., 2019). Providers need to be aware of the potential for high dose THC in those with active inflammation and scarring to increase fibrosis, but also of the potential for CBD to prevent and reduce liver inflammation and scarring, and to advise patients to use CBD-rich cannabis accordingly.

**Other Neurological Disorders**

Recent research highlights the safety and efficacy of using THC, CBD, THCA, CBDA in the treatment of many neurological disorders refractory to conventional treatment such as intractable epilepsy, brain tumors, traumatic brain injury (TBI), Parkinson’s Disease (PD), and Alzheimer’s Disease (AD) and warrants further clinical research (Russo et al., 2018). A 2020 study reported on novel therapeutic approaches to PD and AD that involve modulating the ECS by using FAAH/MAGL inhibitors which prevent breakdown of endocannabinoids and increase levels indirectly. The study found this led to a “reduction in amyloid β-protein deposition and inhibition of the death of dopamine neurons, which are commonly accepted to underlie the pathogenesis of AD and PD, respectively” (Ren et al., 2020).
Other studies on PD show the potential of cannabis to improve symptoms but difficulty in determining which chemovar or cannabinoids are most effective. For example: 49.5% of 339 patients with PD using oral cannabis leaves (CBDA,THCA) for three months improved general function, resting tremor, bradykinesia, and rigidity with few side effects; an open-label observational study of 22 patients with PD smoking cannabis (THC-rich) reported significant improvement in tremor, rigidity, bradykinesia, and also in sleep and pain, with few side effects; and a case series with four pts with PD and REM sleep behavior disorder had prompt and substantial reduction in the frequency of RBD-related events using 75 mg of CBD for 3 pts and 300 mg for one patient (Chagas et al., 2014; Lotan et al., 2014; Venderová et al., 2004).

Research on AD has found that low dose THC can be effective at improving symptoms: 39 pts with agitation in moderate to severe AD using Nabilone (THC) for 14 weeks showed significant reduction in agitation over 6 weeks and greater clinical improvements than similar RCTs using antipsychotics and antidepressants; an open-label pilot study in Israel on 11 patients with AD used 2.5-7.5 mg of THC twice a day and found significant reduction in delusions, agitation, aggression, apathy, sleep and caregiver distress; and a prospective observational study on 10 patients with severe dementia using low dose 1:2 THC/CBD, ~8 mg/16mg per day divided three times a day for two months greatly improved behavior problems, rigidity, and daily care, with some able to stop or decrease their opioids, benzodiazepines, and antipsychotics (Herrmann et al., 2019; Shelef et al., 2016; Broers et al., 2019).

Research on using cannabis to help with TBI is just as promising. A systematic review and meta-analysis on using CBD in experimental stroke showed CBD at time of injury reduced size of brain lesion an average of 20% and reduced early and late impairment (England et al., 2015). A study on preclinical and clinical models for neurodegenerative disorders and
stroke/brain trauma showed CBD 1mg/kg improved vascular supply, reduced inflammation, promoted neurogenesis (Fernández-Ruiz et al., 2015). A preclinical study on mice found short-term CBD 10 mg/kg can reduce neuroinflammation and promote neuroplasticity and functional recovery after brain ischemia reporting that CBD: prevented the cognitive/emotional impairment, attenuated hippocampal neurodegeneration and white matter (WM) injury, and reduced glial response that were induced by bilateral common carotid artery occlusion (BCCAO); in ischemic mice, exhibited an increase in the hippocampal BDNF brain derived neurotrophic factor (BDNF) protein levels; and stimulated neurogenesis and promoted dendritic restructuring in the hippocampus of BCCAO in mice (Mori et al., 2017). Another recent study using piglet models of newborn hypoxic-ischemic brain damage found CBD reduced death of neurons, preserved brain activity, prevented seizures, improved neurobehavioral performance at 72 hours and 30 days after injury, and had synergistic effects with hypothermic treatment (Barata et al., 2019).

**Cancer**

There is conclusive evidence that medical cannabis is safe and effective for reducing symptoms caused by chemotherapy such as nausea, vomiting, anorexia, chronic pain, and insomnia (NASEM, 2017). Many doctors find it safer to use cannabis for these symptoms than writing multiple different prescriptions that may interact with each other or cancer-directed treatment (Abrams et al., 2015).

However, there needs to be caution with claims that cannabis can kill cancer as not enough research proves or recommends this in lieu of conventional treatment. Though cannabis may show potential to kill cancer due to its anti-neoplastic properties, cancer is incredibly complex and so is cannabis with its hundreds of different compounds. There are some preclinical studies that show THC and CBD combined demonstrate anti-cancer properties -- triggering
apoptosis, preventing cell growth and division, preventing angiogenesis, preventing metastasis. (Ladin et al, 2016; López-Valero et al., 2018). There are reports of objective clinical responses in 119 cancer patients given pharmaceutical CBD 10-30 mg twice daily in bursts, three days on and three days off with clinical response in 92% of the cases, but the responses only emerged after six months of treatment (Kenyon et al., 2018). There is also evidence that cannabis may have potential as an adjunct to treatment. A phase II RCT in 21 patients with recurrent glioblastoma used Nabiximols added as adjunct to Temozolomide showing the one-year survival rate was 83% w/ Nabiximols and 56% w/ placebo, with median survival >550 days with Nabiximols versus 369 days with placebo (Twelves et al., 2017).

However, much more research is needed before recommending cannabis to kill cancer, and there are also some cautions for using medical cannabis as an adjunct with immunotherapy. For example, studies using cannabis as an adjunct with Nivolumab show the immunomodulatory effects of cannabis may inhibit effectiveness of cancer immunotherapy (Bar-Sela et al., 2020; Taha et al., 2019). Cannabis clinicians advise patients using immunotherapy who also want to use cannabis to treat symptoms to use only low doses and to skip dosing two days before and five days after injection (Sulak, 2021).

As well, pre-clinical research from Israel demonstrates the complexity of trying to use cannabis to treat cancer and how various compounds in cannabis other than THC and CBD may play a larger role than previously thought. The study used cannabis strains that had similar amounts of THC and CBD but different levels of THCA, CBDA, and CBG. The results found that one strain killed colon cancer cells but had no impact on prostate cancer cells, while another strain killed prostate cancer cells but had no impact on colon cancer cells, revealing that the
minor cannabinoids may be a critical factor in determining how to use cannabis to kill different types of cancer and that further research on these is urgently needed (Baram et al., 2019).

Providers need to be aware that there is conclusive evidence that cannabis is safe and effective for reducing symptoms from chemotherapy and improving quality of life. However, caution needs to be used with immunotherapy and more research is needed before recommending cannabis as an anti-cancer treatment as the effects vary significantly based on the type of cancer and cannabis preparation.

Summary of Current Research

In summary, there is existing and emerging research that demonstrates medical cannabis can have a therapeutic role for improving many conditions patients suffer from in clinical practice such as chronic pain, neuropathic pain, insomnia, inflammation, spasticity, intractable seizures, nausea and vomiting, anxiety, depression, addiction and opioid use disorder, and several neurological disorders refractory to conventional treatment. Cannabis contains over 500 pharmacological and biochemical compounds, of which only a few are understood, so there are likely more potential therapeutic uses that remain undiscovered. More research needs to be done, especially regarding most effective doses and ratios, but there is enough quality evidence to know that medical cannabis is safe and effective and can help many, especially those with conditions refractory to conventional treatment. Providers need to be educated on the benefits, risks, and pharmacology of medical cannabis to realize it can be a powerful tool for providers and patients to use to help many find relief from suffering and improved quality of life.
CHAPTER 9

THESIS RESEARCH

Methodology

This research involves a one-hour presentation on medical cannabis given to medical providers in Maine via live and pre-recorded sessions including a PowerPoint and pre/post survey.

The presentation includes a 50-minute PowerPoint titled “The Medical Use of Cannabis in Clinical Practice” which consists of condensed highlights mostly from the Healer Medical Cannabis Training and Certification program designed by internationally acclaimed cannabis specialist Dr. Dustin Sulak, used with permission. It also contains elements of “The Medical Use of Cannabis” course from The Medical Cannabis Institute which offers accredited online medical cannabis education for healthcare professionals and state-specific certification, developed in collaboration with the Society of Cannabis Clinicians, a group of expert cannabis physicians and scientists, of which Dr. Sulak is also a board member.

The PowerPoint will be narrated in person for the live sessions and by audio recording for the pre-recorded sessions. For those requesting a pre-recorded presentation, the PowerPoint with audio recording and consent/survey packets will be emailed to a clinical coordinator who will forward this information to the providers and medical students.

The presentation also includes a 5-minute anonymous paper survey to be completed immediately prior to and post presentation. The survey consists of Likert-scale questions to gather feedback on providers’ knowledge of medical cannabis and comfort level guiding patients who use it, possible barriers to discussing/recommending medical cannabis with patients, and the impact of the presentation on these barriers (See APPENDIX A: PRE/POST SURVEY). The
survey questions on barriers come from the same survey given to Minnesota oncologists to assess barriers (Zylla et al., 2018) and were used with permission from the study’s leading author, Dylan Zylla.

A consent form will be attached to the front of the paper survey (See APPENDIX B: CONSENT FORM). For the live sessions, this packet with the consent and survey will be distributed immediately prior to presentation and collected immediately post presentation by principal investigator. For pre-recorded sessions, the principal investigator will mail the consent and survey packets to the clinical coordinator who will distribute these packets immediately prior to the participants receiving the pre-recorded sessions and collect them after the session is viewed.

The participants targeted are medical providers who are at least 18 years old and work with patients in clinical practice at all levels (i.e. MD, DO, NP, PA, RN, and RN students). All levels of providers are included, student nurses as well, to maximize participation as well as to gather a wider array of possible barriers to providers discussing cannabis. For example, the concern of legal ramifications or stigma might be more relevant to some levels of providers than others and might therefore benefit from a more targeted intervention at that level. The level of degree, years of practice, and area of practice are the only demographic information that will be gathered on the survey to delineate these differences. Since the presentations are voluntary with no compensation or CME credit, the number of participants is projected to be small, with the total expected number from all sessions being 25-50.

**Results**

There were 24 total participants with six total participants returning their survey -- a response rate of 25%. The results of the survey are below with the percentage of change from pre- to post-survey noted in the right column.
Table. 10.1 Results from pre/post survey.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am familiar with the endocannabinoid system and how it works.</td>
<td>83%</td>
</tr>
<tr>
<td>I am aware that cannabis has ~530 different compounds (120 different</td>
<td>100%</td>
</tr>
<tr>
<td>cannabinoids) in cannabis that each have different pharmacologic effects.</td>
<td></td>
</tr>
<tr>
<td>I am aware there are different preparations of cannabis (i.e. chemovar,</td>
<td>100%</td>
</tr>
<tr>
<td>strains) that vary in their percentage of these compounds most notably</td>
<td></td>
</tr>
<tr>
<td>their ratio of the two major cannabinoids THC:CBD</td>
<td></td>
</tr>
<tr>
<td>I am familiar with which ratios (i.e., higher in THC or CBD, or 1:1) are</td>
<td>83% showed improvement in all</td>
</tr>
<tr>
<td>most effective for these common qualifying conditions:</td>
<td>conditions ranking their familiarity</td>
</tr>
<tr>
<td>Chronic Pain/Neuropathies</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting/Cachexia</td>
<td></td>
</tr>
<tr>
<td>Anxiety/ Depression</td>
<td></td>
</tr>
<tr>
<td>Epilepsy/Seizures</td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis/Spasms</td>
<td></td>
</tr>
<tr>
<td>Addiction/Opioid Reduction and Cessation</td>
<td></td>
</tr>
<tr>
<td>I am aware of the benefits of the major cannabinoids.</td>
<td>100%</td>
</tr>
<tr>
<td>I am aware of the risks of the major cannabinoids.</td>
<td>83%</td>
</tr>
<tr>
<td>I am aware of the potential adverse effects + drug-drug interactions.</td>
<td>83%</td>
</tr>
<tr>
<td>I am aware of best practices to maximize benefit and minimize harm with</td>
<td>100%</td>
</tr>
<tr>
<td>medical cannabis use (i.e., ratio/product selection, no smoking, lowest</td>
<td></td>
</tr>
<tr>
<td>dose, slow titration prn, avoiding tolerance by resensitizing receptors)</td>
<td></td>
</tr>
<tr>
<td>I feel comfortable discussing the risks and benefits of medical cannabis</td>
<td>67%</td>
</tr>
<tr>
<td>with patients.</td>
<td></td>
</tr>
<tr>
<td>I am likely to discuss the use of medical cannabis with patients who</td>
<td>67%</td>
</tr>
<tr>
<td>struggle with the conditions above known to benefit from use.</td>
<td></td>
</tr>
<tr>
<td>Possible barriers to me discussing medical cannabis with patients are:</td>
<td>17% NO RESPONSE ON PRE-</td>
</tr>
<tr>
<td>Products are not FDA approved</td>
<td>SURVEY</td>
</tr>
<tr>
<td>Unsure about risks/benefits</td>
<td>60%</td>
</tr>
<tr>
<td>Inadequate research to justify use</td>
<td></td>
</tr>
<tr>
<td>Concern about abuse/misuse</td>
<td>80%</td>
</tr>
<tr>
<td>Concern about quality/consistency of product</td>
<td></td>
</tr>
<tr>
<td>Unsure about legal ramifications to me</td>
<td>60%</td>
</tr>
<tr>
<td>Unsure about legal ramifications to patient</td>
<td></td>
</tr>
<tr>
<td>Concern about cost to patient</td>
<td>60%</td>
</tr>
<tr>
<td>I don’t want to be identified as one who supports cannabis use</td>
<td></td>
</tr>
<tr>
<td>I am interested in learning more about medical cannabis.</td>
<td>33%</td>
</tr>
</tbody>
</table>

67% improvement; 100% “moderately to extremely comfortable”


**Discussion**

**Limitations of Study**

The results were limited by the small sample size, low response rate of 25%, and the lack of diversity with five of the six surveys coming from the live presentation at Northern Maine Medical Center (NMMC) and one survey coming from the providers at University of Maine Cutler Health Center in Orono who watched a PowerPoint recording of the presentation. This low response rate and lack of diversity was unanticipated and due to poor timing. The presentation was unfortunately delayed and had to be offered during the last week of summer when most providers at Cutler Health were trying to use their summer vacation time before classes started which led to only one provider electing to participate. Perhaps if there were more incentive to watch the presentation like CME credits, more would have participated.

NMMC did have more participants but was still small with twenty-three attending out of sixty who were sent the flyer. As well, the majority elected to participate via zoom due to an unanticipated COVID outbreak that shut down three nearby school systems to ‘remote learning status’ the same day the survey and presentation were being administered. The clinical coordinator had sent an email prior to the presentation with an attached survey, consent form, and reference packet. But only one provider printed the survey out, competed it, and returned it to the clinical coordinator. The clinical coordinator and principal investigator attempted to contact the providers via email as well as in person, but many were not on site or at work due to being off or working the nightshift, and some worked in satellite locations or were medical students unable to be reached.

In hindsight, the fact that the survey was not electronic seemed to be a large hinderance to busy providers returning the survey. In future studies, especially considering the current
COVID pandemic shifting the workplace to remote, the survey should be electronic, possibly through Qualtrex, to allow for remote participation and ease of survey completion on-line.

The results were also limited by the length of the presentation as some providers from Northern Maine Medical Center had to rush back to their patients waiting for them to return from Grand Rounds. One provider repeatedly interrupted the presentation with objections to the topic and questions, some on content just covered, which made it difficult to get through the whole presentation. This provider revealed after the presentation that he wanted more time to be built in for questions and discussion. Some questions were addressed before, during, and after the presentation as time allowed and in follow-up emails from the author. But these responses were only seen by the providers asking the questions, so other providers did not benefit from the seeing the response. As well, there were some excellent questions on pharmacodynamics that were addressed in the presentation but perhaps too quickly and might have been better processed and understood with more time to process and pause for questions. In hindsight, the presentation might have had more of an impact if it was broken into two smaller 30-minute presentations with more time intentionally built in for questions before, during, and after and for follow-up discussion.

The other limitation is due to possible confirmation bias from the principal investigator who admittedly had a personal conflict of interest due to her son using medical cannabis to stop his seizures since age nine. Attempts to mitigate this bias, to avoid looking for results that confirmed the presentation was successful, were made by ensuring the analysis of the results were strictly by the numbers and percentages. However, the bias is still possible and needs to be considered.
Implications of Research

Despite these limitations, the results that were collected did show statistical evidence of the educational intervention being successful at addressing the barriers to providers discussing medical cannabis with their patients. There was also evidence that the presentation had a significant impact on both the providers’ comfort level and likelihood of them guiding their patients use of medical cannabis in the future. This change is most critical to improving patient care with medical cannabis as some guidance is better than none and patients left on their own.

The percentage of providers that improved their comfort level with discussing cannabis was 67%, with 33 % staying at the same comfort level as “moderately comfortable”. This change may seem modest until comparing it with the levels of comfort pre-presentation where 50% of providers reported being “not at all to slightly comfortable discussing cannabis” to post-presentation where 100% of providers reported being “moderately to extremely comfortable discussing cannabis”. This change in mindset, being open to an idea that one was closed off to prior, is often the hardest to change and has the most long-standing ripple effects. Any growth here is significant.

The providers’ willingness to engage in discussions with their patients also increased after the presentation. In fact, pre-presentation results revealed 67% of providers said the likelihood of them discussing medical cannabis with patients was “not at all or slightly likely”. However, post-presentation showed 83% of providers said they would be “moderately to extremely likely” to discuss medical cannabis with their patients, a significant improvement. This improvement in providers’ willingness to guide their patients will also have a significant impact on patients, many of whom are currently on their own experimenting to find their right dose and ratio and are desperate for some guidance from medical providers.
The increase in providers’ confidence with and likelihood of discussing medical cannabis with their patients is correlated with a significant increase in their level of knowledge regarding medical cannabis. Post-presentation, 100% of providers reported an increase in their awareness of cannabis pharmacology, cannabis preparation, best practices to mitigate harm and maximize benefit, with 67% going from “not at all or slightly aware” to “moderately to extremely aware”. As well, 83% of providers reported an increase in their level of awareness of the endocannabinoid system and familiarity with which ratios are most effective for the most common qualifying conditions. Since one of these conditions is opioid use disorder which is causing significant harm to patients and society, this change could have deep and wide-ranging benefits for patients and society.

Providers’ awareness of risks and benefits of medical cannabis use also increased significantly. Post-presentation, 100% of providers reported an increase in their awareness of the benefits of medical cannabis with 100% reporting they were now “moderately to extremely aware”. This is a significant change from pre-presentation where 50% of providers reported they were “not at all to slightly aware” of the benefits. The awareness of the risks and potential adverse effects also increased post-presentation with 83% of providers reported they were “very to extremely aware” of the risks compared to pre-presentation where 50% providers reported they were “not at all to slightly aware”. Since the requirement for medical certification in Maine is for a provider to deem a patient may benefit from use of cannabis and ensure that they discussed the risks and benefits of use, this improvement can also increase the number of future patients receiving medical certification.

The questions on barriers had mixed results sometimes contradicting the participants reported level of increased knowledge and comfort level. This is perhaps due to the phrasing of
the questions and their placement at the end of the survey, as some participants circled the whole row the same, seemingly in a rush, and one did not complete it at all.

However, there are some findings regarding perceived barriers that could highlight a need for further interventions. For example, the barrier that was most often listed for providers discussing cannabis both pre- and post-presentation was their “concern about quality/consistency of products”. This concern largely exists due to the current status of cannabis being federally illegal which prevents federal oversight for products and more pharmaceutical-grade cannabis preparations. Until cannabis is rescheduled, it might help to do a follow up presentation for providers explaining how and where patients can find safe, effective products in Maine that are tested in a third-party laboratory and perhaps listing the places to find rankings of the top companies on-line with the highest quality products.

The other three barriers that providers ranked highly were also directly related to the status of cannabis being Schedule I: inadequate research, products not being FDA approved, and cost to patient. All three of these barriers could be addressed by cannabis no longer being federally illegal, a status that significantly hinders research, access to quality medicine, and prevents the cost being covered from insurance. These barriers highlight the need for providers to advocate for legislation that proposes rescheduling cannabis, such as the recently proposed “Cannabis Administration and Opportunity Act” advocating to remove all cannabis from scheduling to allow regulation and tax (Fandos, 2021). It is estimated that 70% of the American public now support the legalization of cannabis, so if providers could also express their support and advocate for rescheduling, it may be the push needed for legislation to finally pass (Fandos, 2021). The American Association of Nurse Practitioners has a site specifically designated for this purpose called ‘Advocacy Center’ that helps providers easily contact legislators and make
their voices heard on recent legislation, which can be accessed here:

Meanwhile, until cannabis is rescheduled, these barriers do exist and need to be actively countered. For example, one provider in Maine shared their concern about ‘gag orders’, both written and unwritten, where hospitals actively tell providers not to discuss cannabis, saying if they did so, they would lose federal funds due to being a rural health center. The principal investigator attempted to find evidence of this ‘gag order’ in the by-laws or any evidence that showed federal funds ever being withheld. But no evidence was able to be found for either of these by the time of this writing. However, this barrier to discussing and recommending medical cannabis was specifically addressed in the presentation by sharing a slide reviewing the 2000 court case that ruled this speech was protected by the first amendment ‘freedom of speech’ and the 2002 court case confirming this ruling and stating that any move by the government to penalize or investigate a provider for discussing or recommending cannabis was strictly prohibited (Conant vs McCaffrey, 2000; Conant HIV AIDS vs Walters DEA, 2002). Hopefully, with more education on these court rulings, more providers will be aware of their rights to discuss and recommend cannabis and will start actively speaking out against written or unwritten policies trying to intimidate or silence their rights.

Many perceived barriers could also be addressed by future educational presentations, for example “Best practices for guiding patients to find safe and cost-effective medicine”, and “Exploring cannabis educational resources for the most current, high-quality research and evidence-based guidelines”. The results of the surveys made the author more aware of the extent to which most providers lacked knowledge on medical cannabis, with many lacking knowledge on even simple basic understandings of the endocannabinoid system and pharmacodynamics of
the two major cannabinoids that are critical to understanding how medical cannabis works. In hindsight, the providers needed more time to process the information and to ask questions to cement their new understanding of the material presented. Future presentations that break up the delivery into smaller 30-minute presentations that allow more time for questions, processing, and discussions, may have an even greater impact.

**Conclusion**

In summary, millions of patients are using medical cannabis and in need of guidance from their providers, most of whom lack the necessary knowledge and confidence to guide their patients’ use of medical cannabis. However, brief educational presentations for providers on medical cannabis can successfully increase providers’ knowledge on the risks and benefits of medical cannabis. It can also increase providers’ confidence with and likelihood of discussing medical cannabis use with patients. The significance of the results from the educational intervention used here is limited by the small sample size and number of surveys returned, but the overall positive results offer hope for future educational interventions and more patients having guidance from their providers in the future. In fact, 100% of the providers surveyed post-presentation reported they were “moderately to extremely interested” in learning more about medical cannabis. This research has inspired the author to do more presentations on medical cannabis in the future for providers, of shorter duration to allow for questions, both in person and on-line to make it more accessible to providers. Hopefully, future education for providers will result in less patients having to suffer needlessly or having to experiment on their own to find medicine to help them heal with less harm and improved quality of life.
REFERENCES


Patel, J., & Marwaha, R. (2021, July 12). *Cannabis use disorder.* StatPearls [Internet].

Fann, J. R. (2017). Cannabis use among patients at a comprehensive cancer center in a
state with legalized medicinal and recreational use. *Cancer, 123*(22), 4488–4497.
https://doi.org/10.1002/cncr.30879


Pinto, J. V., Saraf, G., Frysch, C., Vigo, D., Keramatian, K., Chakrabarty, T., Lam, R. W.,
Kauer-Sant'Anna, M., & Yatham, L. N. (2020). Cannabidiol as a Treatment for Mood
Disorders: A Systematic Review. *Canadian journal of psychiatry. Revue canadienne de

addictive behaviors: a systematic review of the evidence." *Substance abuse: research and
treatment 9*, SART-S25081

cannabis concentrates and cannabinoid transfer during the act of dabbing. *The Journal of
Toxicological Sciences, 40*(6). https://doi.org/10.2131/jts.40.797

Rapaport, L. (2019, February 6). Chronic pain - most common reason U.S. patients get medical
idUSKCN1PV2O1.

system agents in neuropsychiatric and neurodegenerative diseases—focusing on
https://doi.org/10.1038/s41401-020-0385-7

in Childhood Epilepsy in pediatric patients enrolled in a prospective, open-label clinical
study with cannabidiol. *Epilepsia, 58*(8), e96–e100. https://doi.org/10.1111/epi.13815

Ryan, J. E., McCabe, S. E., & Boyd, C. J. (2021). Medicinal cannabis: Policy, patients, and
providers. *Policy, Politics, & Nursing Practice, 22*(2), 126–133.
https://doi.org/10.1177/1527154421989609

https://doi.org/10.1542/peds.2018-1889


APPENDIX A: PRE/POST SURVEY

Degree/s: _______  Years of Practice: _______  Area/s of Practice: _______________________

Please rate the following statements pre and post presentation, from 1-5.  
(1 = Not at all, 2 = Slightly, 3 = Moderately, 4 = Very, 5 = Extremely)

<table>
<thead>
<tr>
<th>Statement</th>
<th>PRE</th>
<th>POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am familiar with the endocannabinoid system and how it works.</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I am aware that cannabis has over 530 different compounds (120 different cannabinoids) that each have different pharmacologic effects.</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I am aware there are different preparations of cannabis (chemovar/strains) that vary in their percentage of these compounds, most notably their ratio of the two major cannabinoids THC:CBD</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I am familiar with which ratios (i.e., THC-rich, CBD-rich, 1:1 equal ratio) are most effective for the common qualifying conditions: Chronic Pain/Neuropathies</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Anxiety/ Depression</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Epilepsy/Seizures</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Multiple Sclerosis/Spasms</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Addiction/Opioid Reduction and Cessation</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I am aware of the benefits of the major cannabinoids.</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I am aware of the risks of the major cannabinoids.</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I am aware of the potential adverse effects of cannabis use.</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I am aware of best practices to maximize benefit + minimize harm with medical cannabis (i.e., ratio/product selection, no smoking, lowest dose, slow titration, avoiding tolerance by resensitizing receptors)</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I feel comfortable discussing the risks and benefits of medical cannabis with patients.</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>I am likely to discuss the use of medical cannabis with patients who struggle with conditions known to benefit from use.</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>
Possible barriers to me discussing medical cannabis use with patients are:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products are not FDA approved</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Unsure about risks/benefits</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Inadequate research to justify use</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Concern about misuse/abuse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Concern about quality/consistency of product</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Unsure about legal ramifications to me</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Unsure about legal ramifications to patient</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Concern about cost to patient</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I don’t want to be identified as one who supports cannabis use</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

I am interested in learning more about medical cannabis.         | 1 | 2 | 3 | 4 | 5 |
APPENDIX B: CONSENT FORM

CONSENT FORM FOR ANONYMOUS SURVEY
You are invited to participate in a research project being conducted by Arianne Kryskow a graduate student in the Family Nurse Practitioner program at the University of Maine School of Nursing with assistance from Dr. Patricia Poirier, Professor of Nursing. The purpose of the research is to assess the need for and benefit of medical cannabis education for medical providers. You must be at least 18 years of age to participate.

What Will You Be Asked to Do?
If you decide to participate, you will be asked to view a 45-minute educational PowerPoint and to complete an anonymous 5-minute survey immediately prior to and following the PowerPoint, total time estimated at 1 hour. The survey will ask you to rate statements such as “I am aware of the risks and benefits of the major cannabinoids” and “I am aware of the contraindications for medical cannabis use” on a Likert-type scale of 1-5 with 1 being “Not at all” and 5 being “Extremely”. For those viewing the presentation live, you will return the survey immediately after the presentation to Arianne Kryskow. For those viewing prerecorded sessions, please return the survey immediately after viewing recording to Mr. Sean Sibley.

Risks
Except for your time and inconvenience, there are no risks to you from participating in this study.

Benefits
This presentation will increase your knowledge of medical cannabis use (i.e. current research on the clinical utility, risks and benefits, contraindications, strategies to maximize benefit and minimize harm) and your comfort level with guiding patients who use medical cannabis. This study will also help inform the need for and benefit of future medical cannabis education for medical providers.

Confidentiality
This study is anonymous. Please do not write your name on the survey. There will be no records linking you to the data. Surveys will be stored in a locked drawer and the data aggregated in a password-protected computer. All data will be destroyed by December 20, 2021.

Voluntary
Participation is voluntary. If you choose to take part in this study, you may stop at any time. You may skip any questions you do not wish to answer. Submission of the survey implies consent to participate.

Contact Information
If you have any questions about this study, please contact Arianne Kryskow at 207-436-0483 or arikryskow@gmail.com You may also reach the faculty advisor on this study at patricia.poirier@maine.edu. If you have any questions about your rights as a research participant, please contact the Office of Research Compliance, University of Maine, 207-581-2657 (or e-mail umric@maine.edu).
## APPENDIX C: CERTIFICATE OF ANALYSIS (COA). Edited Sample.

<table>
<thead>
<tr>
<th>ID</th>
<th>Weight %</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9-THC</td>
<td>0.140</td>
<td>1.32</td>
</tr>
<tr>
<td>THCV</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CBD</td>
<td>4.17</td>
<td>39.3</td>
</tr>
<tr>
<td>CBDV</td>
<td>0.0298</td>
<td>0.281</td>
</tr>
<tr>
<td>CBG</td>
<td>0.0507</td>
<td>0.478</td>
</tr>
<tr>
<td>CBC</td>
<td>0.159</td>
<td>1.50</td>
</tr>
<tr>
<td>CBN</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>THCA</td>
<td>0.0169</td>
<td>0.159</td>
</tr>
<tr>
<td>CBDA</td>
<td>0.674</td>
<td>6.36</td>
</tr>
<tr>
<td>CBGA</td>
<td>0.0131</td>
<td>0.124</td>
</tr>
<tr>
<td>D8-THC</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>exo-THC</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Total**
- 5.25
- 49.5
- 0%

**Cannabinoids (wt%)**
- 4.2%

### Ratio of Total CBD to THC 30.7:1

<table>
<thead>
<tr>
<th>ID</th>
<th>Weight %</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9-THC</td>
<td>0.140</td>
<td>1.32</td>
</tr>
<tr>
<td>THCV</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CBD</td>
<td>4.17</td>
<td>39.3</td>
</tr>
<tr>
<td>CBDV</td>
<td>0.0298</td>
<td>0.281</td>
</tr>
<tr>
<td>CBG</td>
<td>0.0507</td>
<td>0.478</td>
</tr>
<tr>
<td>CBC</td>
<td>0.159</td>
<td>1.50</td>
</tr>
<tr>
<td>CBN</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>THCA</td>
<td>0.0169</td>
<td>0.159</td>
</tr>
<tr>
<td>CBDA</td>
<td>0.674</td>
<td>6.36</td>
</tr>
<tr>
<td>CBGA</td>
<td>0.0131</td>
<td>0.124</td>
</tr>
<tr>
<td>D8-THC</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>exo-THC</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Total**
- 5.25
- 49.5
- 0%

**Cannabinoids (wt%)**
- 4.2%

### Limit of Quantitation (LOQ) = 0.0111 wt%

---

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Metal</th>
<th>Conc. (µg/kg)</th>
<th>RL Use Limits 2 (µg/kg)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>As</td>
<td>Arsenic</td>
<td>ND</td>
<td>50.0</td>
<td>200 1,500 PASS</td>
</tr>
<tr>
<td>Cd</td>
<td>Cadmium</td>
<td>ND</td>
<td>50.0</td>
<td>200 500 PASS</td>
</tr>
<tr>
<td>Hg</td>
<td>Mercury</td>
<td>ND</td>
<td>50.0</td>
<td>100 1,500 PASS</td>
</tr>
<tr>
<td>Pb</td>
<td>Lead</td>
<td>ND</td>
<td>50.0</td>
<td>500 1,000 PASS</td>
</tr>
</tbody>
</table>

**84697-HM**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Analysis</th>
<th>Results</th>
<th>Units</th>
<th>Limits*</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>Total Aerobic Bacterial Count</td>
<td>&lt;1,000</td>
<td>CFU/g</td>
<td>100,000 CFU/g</td>
<td>PASS</td>
</tr>
<tr>
<td>CC</td>
<td>Total Coliform Bacterial Count</td>
<td>&lt;100</td>
<td>CFU/g</td>
<td>1,000 CFU/g</td>
<td>PASS</td>
</tr>
<tr>
<td>EB</td>
<td>Total Bile Tolerant Gram Negative Count</td>
<td>&lt;100</td>
<td>CFU/g</td>
<td>1,000 CFU/g</td>
<td>PASS</td>
</tr>
<tr>
<td>YM</td>
<td>Total Yeast &amp; Mold</td>
<td>&lt;1,000</td>
<td>CFU/g</td>
<td>10,000 CFU/g</td>
<td>PASS</td>
</tr>
</tbody>
</table>

**84697-MB1**
### 85204-VC

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th>Amount</th>
<th>Limit</th>
<th>RL</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propane</td>
<td>74-98-6</td>
<td>ND</td>
<td>1,000 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Isobutane</td>
<td>75-28-5</td>
<td>ND</td>
<td>1,000 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Butane</td>
<td>106-97-8</td>
<td>ND</td>
<td>1,000 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Methanol</td>
<td>67-56-1</td>
<td>ND</td>
<td>3,000 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Ethanol</td>
<td>64-17-5</td>
<td>2,920 ppm</td>
<td>5,000 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Acetone</td>
<td>67-64-1</td>
<td>ND</td>
<td>5,000 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>67-63-0</td>
<td>337 ppm</td>
<td>5,000 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>75-05-8</td>
<td>ND</td>
<td>410 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Hexane</td>
<td>110-54-3</td>
<td>ND</td>
<td>290 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
<tr>
<td>Heptane</td>
<td>142-82-5</td>
<td>ND</td>
<td>5,000 ppm</td>
<td>100</td>
<td>PASS</td>
</tr>
</tbody>
</table>

### 84697-PST

<table>
<thead>
<tr>
<th>Analyte</th>
<th>CAS</th>
<th>Result</th>
<th>Units</th>
<th>LLD</th>
<th>Limits (ppb)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abamectin</td>
<td>71751-41-2</td>
<td>ND</td>
<td>ppb</td>
<td>0.20</td>
<td>300</td>
<td>PASS</td>
</tr>
<tr>
<td>Spinosad</td>
<td>168316-95-8</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>3000</td>
<td>PASS</td>
</tr>
<tr>
<td>Pyrethin</td>
<td>8003-34-7</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>1000</td>
<td>PASS</td>
</tr>
<tr>
<td>Trifloxystrobin</td>
<td>141517-21-7</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>300000</td>
<td>PASS</td>
</tr>
<tr>
<td>Spirotetramat</td>
<td>203313-25-1</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>13000</td>
<td>PASS</td>
</tr>
<tr>
<td>Spiromesifen</td>
<td>283594-90-1</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>12000</td>
<td>PASS</td>
</tr>
<tr>
<td>Piperonyl butoxide</td>
<td>51-03-6</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>80000</td>
<td>PASS</td>
</tr>
<tr>
<td>Paclobutrazol</td>
<td>76738-62-0</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>10</td>
<td>PASS</td>
</tr>
<tr>
<td>Myclobutanil</td>
<td>88671-89-0</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>9000</td>
<td>PASS</td>
</tr>
<tr>
<td>Imidacloprid</td>
<td>138261-41-3</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>3000</td>
<td>PASS</td>
</tr>
<tr>
<td>Imazalil</td>
<td>35554-44-0</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>10</td>
<td>PASS</td>
</tr>
<tr>
<td>Fenoxycarb</td>
<td>72490-01-8</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>10</td>
<td>PASS</td>
</tr>
<tr>
<td>Etoxazole</td>
<td>153233-91-1</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>1500</td>
<td>PASS</td>
</tr>
<tr>
<td>Dichlorvos</td>
<td>62-73-7</td>
<td>ND</td>
<td>ppb</td>
<td>3.00</td>
<td>10</td>
<td>PASS</td>
</tr>
<tr>
<td>Cylpyriphos</td>
<td>68359-37-5</td>
<td>ND</td>
<td>ppb</td>
<td>0.50</td>
<td>1000</td>
<td>PASS</td>
</tr>
<tr>
<td>Bifenthrin</td>
<td>82657-04-3</td>
<td>ND</td>
<td>ppb</td>
<td>0.20</td>
<td>500</td>
<td>PASS</td>
</tr>
<tr>
<td>Bifenazate</td>
<td>149877-41-8</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>5000</td>
<td>PASS</td>
</tr>
<tr>
<td>Azoxyystrobin</td>
<td>131860-33-8</td>
<td>ND</td>
<td>ppb</td>
<td>0.10</td>
<td>40000</td>
<td>PASS</td>
</tr>
</tbody>
</table>
BIOGRAPHY OF THE AUTHOR

Arianne Kryskow lives in Fort Kent, Maine with her husband and two children. She has over twenty years of experience as an English teacher and guidance counselor in Maine and loved helping children and families. However, after witnessing how medical cannabis stopped her son’s seizures completely, Arianne recently switched her career to the medical field to help other families access cannabis. She attended the University of Maine in Fort Kent to receive her Accelerated Nursing Degree in the summer of 2018 and entered the Family Nursing Practitioner program at The University of Maine in Orono in the fall 2018. Arianne aspires to work in an integrative health clinic where she can help people find healing and quality of life on their own terms. Arianne is a candidate for the Master of Science degree in Nursing from the University of Maine in December 2021.