



# JOURNAL OF NURSING REGULATION

*Advancing Nursing Excellence for Public Protection*

## **The NCSBN National Nursing Guidelines for Medical Marijuana**

Current Legislation, Scientific Literature Review, and Nursing Implications

Nursing Care of the Patient Using Medical Marijuana

Medical Marijuana Education in Pre-Licensure Nursing Programs

Medical Marijuana Education in APRN Nursing Programs

APRNs Certifying a Medical Marijuana Qualifying Condition



**NCSBN**  
**GUIDELINES** FOR THE **NURSING CARE** OF  
Patients Using Marijuana

The NCSBN National Nursing Guidelines  
for Medical Marijuana



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# The NCSBN National Nursing Guidelines for Medical Marijuana

Prior to 1936, cannabis was sold over the counter and used commonly for a variety of illnesses in the United States (Marijuana Policy Project, 2014). By 1936, every state had passed a law to restrict possession of cannabis, thus eliminating its availability as an over-the-counter drug. Then in 1970, the Comprehensive Drug Abuse Prevention and Control Act (1970) provided a classification of controlled substances; cannabis was included in the list of Schedule I Controlled Substances, thereby continuing the prohibition of the use of cannabis by prohibiting health care practitioners from prescribing cannabis.

Use of cannabis remained restricted until the first legalization of medical marijuana was approved by voters in California in 1996. Even after the voters' approval, the federal government opposed the proposition and threatened to revoke the prescription-writing abilities of doctors who recommended or prescribed marijuana. It was not until 2000 that a group of physicians challenged this policy and prevailed in court, and a decision was made to allow physicians to recommend—but not prescribe—medical marijuana (Marijuana Policy Project, 2014).

Since then, an increasing cultural acceptance of cannabis has prompted 31 jurisdictions (including the District of Columbia), Guam, Puerto Rico (National Conference of State Legislatures [NCSL], 2017), and all provinces/territories of Canada (Government of Canada, 2016) to pass legislation legalizing medical cannabis. In these laws, the jurisdiction has adopted exemptions legalizing the use of cannabis for medical purposes. An increasing proportion of jurisdictions have also decriminalized and legalized recreational cannabis use.

The use of either medical or recreational cannabis raises evolving public health, nursing practice, science, legal, education, ethical, and social issues. Of significance, there is a contradiction between the federal law classifying cannabis as a Schedule I Controlled Substance and various states legalizing its use medically, recreationally, or both. This federal classification has prevented open and unlimited research on cannabis. As a result, research on the efficacy of cannabis for treatment of certain medical conditions is limited and lacking. Specifically, the research has not definitively specified indications, dosage, route, safety, adverse effects, and long-term effects of cannabis.

Without evidence that is scientifically rigorous, statistically reportable, and based on patient populations, nurses will face increasing challenges concerning medical cannabis. To address the lack of guidelines for nurses when caring for individuals utilizing cannabis, the National Council of State Boards of Nursing Board of Directors appointed members to the Medical Marijuana Nursing Guidelines Committee (see Appendix A). In order to create the requested guidelines and recommendations for education and care, a review of the relevant statistics, current legislation, scientific literature, and clinical research on cannabis as a therapeutic agent was required. The Committee also consulted known experts in the area of medical marijuana, its use, safety, and legislation. This report documents the results of this work and presents this important information in two parts. Part I presents the results of these reviews and consultations; Part II presents the specific Guidelines created by the Committee: nursing care of the patient using medical marijuana, medical marijuana education in pre-licensure nursing programs, medical marijuana education in APRN nursing programs, and APRNs certifying a medical marijuana qualifying condition.

# Current Legislation, Scientific Literature Review, and Nursing Implications

The surge of cannabis legislation has outpaced research on the use of cannabis due to the restrictions placed on that research as a result of its classification as a Schedule I Controlled Substance (Comprehensive Drug Abuse Prevention and Control Act, 1970). Nurses are left without evidence-based resources when caring for patients who use medical or recreational cannabis products. Research is possible, but only under rigorous oversight from the government. The process for obtaining cannabis for federally funded research purposes is cumbersome and unlike any other procedures for drug research.

Importantly, the reader must be aware that cannabis as a therapeutic agent has not been reviewed by the U.S. Food & Drug Administration (FDA) to determine if it is safe or effective and therefore is not subject to the quality standards and safety information collection standards that are applicable to most prescription drugs. This report provides a means to inform nurses about the current scientific literature regarding medical use of cannabis as well as areas that currently lack scientific evidence.

It was not until 1973 that scientists discovered how cannabis functioned within the body – as a component of the endocannabinoid system. The endocannabinoid system consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids (Mackie, 2008). These cannabinoid receptors are evident throughout the body, embedded in cell membranes thought to promote homeostasis. Endocannabinoids are naturally occurring substances within the body, while phytocannabinoids are plant substances found in cannabis that stimulate cannabinoid receptors. The most well known of these phytocannabinoids is tetrahydrocannabinol (THC); however cannabidiol (CBD) and cannabitol (CBN) are also gaining attention (Pacher, Batkai, & Kunos, 2006).

Notwithstanding the restrictions resulting from the classification of cannabis as a Schedule I Controlled Substance, high-quality clinical evidence has emerged that establishes the efficacy of cannabis for certain therapeutic applications. However, despite studies describing the value of cannabis in the treatment of certain conditions, its safety has not been fully established by large-scale, randomized clinical trials. Some safety information does exist for cannabis (Ware et al., 2015), but the current research does not fully encompass all available formulations of cannabis or conditions and populations treated with cannabis. Thus, the current evidence for the efficacy and safety of cannabis and cannabinoids has narrow application. For the majority of qualifying conditions typically included in a jurisdiction's medical marijuana program, sufficient experimental evidence does not exist to reasonably demonstrate the therapeutic efficacy, especially for long-term use. Additionally, there is a lack of evidence regarding the numerous strains and preparations of cannabis available as well as its comparative efficacy to standard medications, dosage, tolerability, and safety. Without additional large-scale clinical studies, cannabis remains a complementary and alternative medicine, a drug of last resort, or salvage therapy. It is the hope of many researchers and medical organizations that future research will be less restricted and therefore allow more scientific evidence to elucidate well-founded dosages, delivery routes, and indications. (This report uses many terms related to cannabis and medical marijuana and their programs. See Table 1 for a list of definitions used in this report).

---

TABLE 1

## Definitions of Terms Used in This Report

**Authorize.** Any act of certification, attestation, or other method for a practitioner to affirm that a patient may benefit from medical cannabis. This is explicitly not a prescription.

**Cannabis.** Any raw preparation of the leaves or flowers from the plant genus *Cannabis*. This report uses “cannabis” as a shorthand that also includes cannabinoids.

**Cannabidiol (CBD).** A major cannabinoid that indirectly antagonizes cannabinoid receptors, which may attenuate the psychoactive effects of tetrahydrocannabinol.

**Cannabinoid.** Any chemical compound that acts on cannabinoid receptors. These include endogenous and exogenous cannabinoids.



**Cannabinol (CBN).** A cannabinoid more commonly found in aged cannabis as a metabolite of other cannabinoids. It is nonpsychoactive.

**Certify.** For the purpose of this report, to “certify” is the act of confirming that a patient has a qualifying condition. Many jurisdictions use alternative phrases, such as “attest” or “authorize”; however, 13 of 29 jurisdictions use “certify” language in their statutes.

**Clinical research.** For the purpose of this report, “clinical research” involves studies that experimentally assign randomized human participants to one or more drug interventions to evaluate the effects on health outcomes. Contrasted with **Preclinical research or studies**, which experimentally or observationally use animal models, cell cultures, and/or biochemical assays to determine possible biological effects of an intervention. These studies also include observational studies of human participants that do not control interventions.

**Designated caregiver.** An individual who is selected by the Medical Marijuana Program qualifying patient and authorized by the Medical Marijuana Program to purchase and/or administer cannabis on the patient’s behalf. Also sometimes referred to as an “alternate caregiver.”

**Dronabinol.** The generic name for synthetic tetrahydrocannabinol. It is the active ingredient in the Food & Drug Administration (FDA)-approved drug Marinol (FDA, August 2017).

**Endocannabinoid system.** A system that consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids (Mackie, 2008).

**Marijuana.** A cultivated cannabis plant, whether for recreational or medicinal use. The words “marijuana” and “cannabis” are often used interchangeably in various lay and scientific literature. This report will primarily use the word “cannabis” as a shorthand that also includes cannabinoids. When referring to a medical marijuana program, this report will use the word “marijuana,” as it is often used within program references.

**Medical Marijuana Program (MMP).** The official jurisdictional resource for the use of cannabis for medical purposes. Search the jurisdiction’s website or Department of Health for “medical cannabis program” or “medical marijuana program” (National Conference of State Legislatures, 2017).

**Nabilone.** The generic name for a synthetic cannabinoid similar to tetrahydrocannabinol. It is the active ingredient in the U.S. Food & Drug Administration’s (FDA)-approved drug Cesamet (FDA, 2006).

**Schedule I Controlled Substances.** Defined in the federal Controlled Substances Act as those substances that have a high potential for abuse; no currently accepted medical use in treatment in the United States; and a lack of accepted safety for use of the substance under medical supervision.

**Tetrahydrocannabinol (THC).** One of many cannabinoids found in cannabis. THC is believed to be responsible for most of the characteristic psychoactive effects of cannabis (U.S. Department of Transportation, National Highway Traffic Safety Administration, 2017).

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## Federal and State Legislation Through 2018

Over the past few decades, the federal government and individual states have instituted varying legal approaches regarding the availability and dispensing of cannabis for medical purposes.

### Federal Legislation and Actions

The U.S. federal government, through Title 21 United States Code (Comprehensive Drug Abuse Prevention and Control Act, 1970), has the authority to evaluate drugs and other substances. This law was enacted to protect the public, stating: “illegal importation, manufacture, distribution, and possession and improper use of controlled substances have a substantial and detrimental effect on the health and general welfare of the American people.”

Substances classified as Schedule I Controlled Substances are considered to have no accepted medical value and present a high potential for abuse. Cannabis and its derivatives have been classified as Schedule I Controlled Substances since the enactment of the Controlled Substance Act in 1970. This Drug Enforcement Administration (DEA) classification not only prohibits practitioners from prescribing cannabis; it also prohibits most research using cannabis except under rigorous oversight from the government’s National Institute on Drug Abuse.

The process for obtaining cannabis for federally funded research purposes is cumbersome and unlike any other drug research. Currently, the only legal source of cannabis for research purposes is grown in limited quantities at the University of Mississippi (National Institute on Drug Abuse [NIDA], May 2017). The DEA sets a quota for the amount of cannabis that can be grown for research studies (Drug Enforcement Administration [DEA], 2017). Applications to use this source of cannabis must be made to the FDA, DEA, and National Institute on Drug Abuse (NIDA, March 2017).

Although the use of marijuana pursuant to authorized medical marijuana programs (MMPs) conflicts with federal law and regulations, at present there is no controlling case law holding that Congress intended to preempt the field of regulation of cannabis use under its supremacy powers (*Beek v. City of Wyoming*, 2014; Mikos, 2012).



The federal government's position on prosecuting the use of cannabis that is legal under the law of the applicable jurisdiction has been set out in U.S. Department of Justice (DOJ) position papers. In 2009, the U.S. Attorney General took a position that discouraged federal prosecutors from prosecuting people who distribute or use cannabis for medical purposes in compliance under the law of the applicable jurisdiction (U.S. Department of Justice [DOJ], 2009); further similar guidance was given in 2011, 2013, and 2014 (DOJ, 2011, 2013, 2014). In January 2018, the U.S. Office of the Attorney General rescinded the previous nationwide guidance specific to marijuana enforcement (DOJ, 2018). The 2018 memorandum provides that federal prosecutors follow the well-established principles in deciding which cases to prosecute, namely, the prosecution is to weigh all relevant considerations, including priorities set by the attorneys general, seriousness of the crime, deterrent effect of criminal prosecution, and cumulative impact of particular crimes on the community.

Numerous federal bills have been introduced in recent years in an effort to reschedule cannabis to allow more research, but as of 2017, none of these bills passed the House of Representatives or the Senate (S. 683, 2015; H.R. 1013, 2015; H.R. 715, 2017; H.R. 1227, 2017; H.R. 1841, 2017).

In 2016, congressional representatives called on the DEA to reschedule cannabis (Bernstein, 2016). The FDA requested a scientific and medical evaluation and scheduling recommendation from the Department of Health and Human Services (HHS) (Rosenberg, 2016a). HHS concluded that "marijuana has a high potential for abuse, has no accepted medical use in the United States, and lacks an acceptable level of safety for use even under medical supervision" (DEA, 2016, August 12). The DEA denied petitions to reschedule cannabis as a Schedule II Controlled Substance (drugs with a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions due to the high potential for abuse, which may lead to severe psychological or physical dependence) or lower, stating that cannabis will remain a Schedule I Controlled Substance because the DEA considers cannabis to have a high potential for abuse with no medical benefit (Rosenberg, 2016b). However, the DEA recognized the lack of scientific study on cannabis and announced a policy change, which expanded the number of DEA-registered cannabis manufacturers (Rosenberg, 2016a). This should provide for an increased supply of cannabis for FDA-authorized research purposes. Despite this policy change, the DEA has yet to approve any application to become a licensed producer of cannabis for research (Joseph, 2017). Researchers hoping to study the medical effects of cannabis face a protracted wait time for plant material. The plant material that they do receive contains a substantially lower quantity of cannabinoids than the wide variety of that is available through dispensaries, limiting the applicability of research results (Vergara et al., 2017). This federal bottleneck and low cannabis quality stymie and effectively hinder new and available studies.

### **State Legislation and Actions**

Summarizing the specifics of each jurisdiction's medical marijuana legislation is difficult because there are few commonalities among MMPs (Bestrashniy & Winters, 2015). The practitioner should review the unique characteristics of a jurisdiction's MMP (NCSL, 2017). The relevant statute is most easily located through the jurisdiction's Department of Health and MMP; useful links are provided through the National Council of State Legislatures (NCSL, 2017).

Since the first MMP in California (Compassionate Use Act of 1996), the trend among states is toward legalizing cannabis for medical use (Halperin, 2016). In 15 states, the public initiated the MMP legislation and ratified it by a ballot measure (ProCon.org, 2017). More recently, medical cannabis laws were passed by state legislatures (ProCon.org, 2017).

MMPs include various provisions regarding the process for procuring a certification for the use of cannabis as well as the amount of cannabis distributed to an individual, and legal protections extended to patients, designated caregivers, and health care providers (NCSL, 2017). MMPs each create a list of qualifying conditions for the use of cannabis (NCSL, 2017). MMPs operate on the best available scientific information, which is limited by the restrictions on cannabis research. Therefore, many qualifying conditions were likely included because of promising preclinical research (this includes research on animals and isolated cellular/tissue samples).

Some MMPs require a bona fide health care provider-patient relationship in order to certify a patient as having a qualifying condition. Other MMPs require a preexisting and ongoing relationship with the patient as a treating health care provider, while some note that the relationship may not be limited to issuing a written certification for the patient or a consultation simply for that purpose. Additionally, a few MMPs specify that an advanced practice registered nurse (APRN) can certify a qualifying condition (NCSL, 2017). Some MMPs require a specific course or training in order for a provider to participate in certifying an MMP qualifying condition (NCSL, 2017).

Patients with a certification of a qualifying condition must register with the local MMP. A registered patient can obtain cannabis from a jurisdiction-authorized cannabis dispensary. Procurement and administration of cannabis for medical purposes are limited to the patient and/or the patient's designated caregiver. The MMP will specify whether designated caregivers are permissible as well as the applicable process for registration as a designated caregiver (NCSL, 2017). In some jurisdictions, the MMP allows an

employee of a hospice provider or nursing or medical facility, or a visiting nurse, personal care attendant, or home health aide to act as a designated caregiver for the administration of medical marijuana (NCSL, 2017).

As Table 2 demonstrates, jurisdictional legislation regarding cannabis is an ever-evolving process. This summary is current as of June 2018.

TABLE 2

### Cannabis Legislation Through June 2018

Type of Provision	Jurisdictions
MMP	AK, AR, AZ, CA, CO, CT, DC, DE, FL, HI, IL, LA*, MA, MD, ME, MI, MN, MT, ND, NH, NJ, NM, NV, NY, OH, OR, PA, RI, VT, WA, WV
Allow cannabidiol products (often for intractable seizures; often the use is restricted to clinical studies)	AL, GA, IA, IN, KY, MO, MS, NC, OK, SC, TN, TX, UT, VA, WI, WY
Allow APRNs to certify a qualifying condition referred to in medical marijuana statute	HI, ME, MA, MN, NH, NY, VT, WA
No cannabis statutes	ID, KS, NE, SD
Recreational use of cannabis	AK, CA, CO, DC, MA, ME, NV, OR, VT, WA

Note. MMP = Medical Marijuana Program; APRN = advanced practice registered nurse.

\* Louisiana lacks the necessary infrastructure to enact its MMP and the state's previous statutory language failed to grant necessary protections to physicians and users. Legislators have yet to decide who will be the legal cultivators for the state and how to regulate pharmacies that will distribute medical cannabis.

Many qualifying conditions (see Table 3) were likely included in MMPs because of promising preclinical research. Some qualifying conditions are likely included only because of symptoms they share with better-studied conditions. A few broad qualifying conditions/symptoms, notably chronic pain, neuropathies, and nausea/vomiting, are the most researched and commonly associated with medical cannabis.

TABLE 3

### Most Common Qualifying Conditions

Although there are 57 qualifying conditions included among the different jurisdictional laws, the most common qualifying conditions across all MMPs are:

- ALS
- Alzheimer's disease
- Arthritis
- Cachexia
- Cancer
- Crohn's disease and other irritable bowel syndromes
- Epilepsy/seizures
- Glaucoma
- Hepatitis C
- HIV/AIDS
- Nausea
- Neuropathies
- Pain
- Parkinson's disease
- Persistent muscle spasms (including multiple sclerosis)
- Posttraumatic stress disorder
- Sickle cell disease
- Terminal illness

Registered medical marijuana patients in two states cite chronic pain as the primary condition they are treating (81% of Arizona patients and 23% of New Jersey patients) (Arizona Department of Health Services, 2016; New Jersey Department of Health, 2016). In Colorado, 93% of patients report pain, regardless of whether it is the primary condition being treated (Colorado Department of Public Health & Environment, 2016).

### Literature Review

There are many reports and reviews of the medical cannabis literature. The National Academy of Sciences (National Academies, 2017) and the World Health Organization (WHO; Madras, 2015) published the two most prominent and thorough reports. The former relies heavily on published high-quality meta-analyses, particularly that of Whiting and colleagues (2015).

The National Academy of Sciences determined that there is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain, chemotherapy-induced nausea and vomiting, and spasticity due to multiple sclerosis (MS). It also reported evidence exists to support the conclusion that cannabis is effective for "improving short-term sleep outcomes

in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis” (National Academies, 2017).

The reports published by the National Academy of Sciences and WHO broadly addressed the evidence for the effectiveness of medical cannabis. However, these two reports did not highlight material immediately useful for practicing health care workers, such as dosage, administration, drug interactions, jurisdiction statutes, and evidence supporting jurisdictional qualifying conditions. Without a nuanced examination of the studies that comprise, or were omitted from, the meta-analyses, details relevant to the care of patients with medical cannabis may be overlooked.

### **Gaps in Comprehensive Reviews**

All analyses and reviews have limitations that may include their stated goals, search terms, search resources, and other methodology (Berlin & Golub, 2014). This report combines a systematic search of the literature using a grading methodology with the intent of summarizing the existing evidence for the current qualifying conditions spread across jurisdictions. The methodology adopted for this report aims to avoid the limitations of previous reviews and compile evidence for legally permissible uses of medical cannabis. One example of a limitation is the grouping or collapsing of terminology regarding psychoses. In the cannabis literature, “psychosis” is frequently applied as an umbrella term to include any of the following, together or separately: psychotic episodes, mania, paranoia, schizophrenia, bipolar disorder, and suicidal ideation (National Academies, 2017). Using “psychosis” in such a general manner reduces the ability to make meaningful conclusions and more often results in improper phrasing of conclusions. This imprecise word choice can impart an effect that is not borne out by the research, but feeds the growing body of anecdotal information and misinformation (de Graaf, 2017; Moffat, Jenkins, & Johnson, 2013). Care is taken in this review to explicitly differentiate between causative, correlative, suggestive, conclusive, insufficient, and mixed evidence.

### **Therapeutic Effects of Cannabis (Literature last updated February 2018)**

This review of the literature began by searching all scholarly articles related to cannabis and its derivatives and the qualifying conditions listed by jurisdictions. This search used medical and scientific as well as gray literature sources (sources outside of traditional academic publishing). The first step identified the most recent and most cited meta-analyses and systematic reviews. The identified citations were reviewed and graded. Citations were reviewed in this manner for every article read until the literature had been exhausted. Additional searches in PubMed and the gray literature were carried out using terms relating to qualifying conditions, common symptoms related to qualifying conditions, and words related to cannabis. Recent reviews and meta-analyses provided a reliable network of cited articles that constitute the core literature. After amassing citations, randomized placebo-controlled studies became the focus for review. These studies are the most likely to elucidate causality in treatments and are the only trusted source of evidence for clinical interventions.

Each study was evaluated using the GRADE scale (Cochrane Methods Bias, n.d.; “What is GRADE?,” 2012), a tool for assessing the quality of evidence, elucidating high, moderate, low, and very low evidence quality. All randomized experimental studies are initially rated as high quality; observational studies began at low-quality rating (and thus do not meet the qualifications for inclusion in this review). In this assessment, a study loses quality if it has serious risk of bias (from improper blinding of subjects and assessors, nonrandom sorting, patient dropout), confounding factors, imprecision, or inconsistency. Studies gain quality if the data show a large effect or dosage effect, or the study adequately controlled confounding factors. See Appendix B, Quality Research, Evidence of Effectiveness of Medical Cannabis presenting moderate-to high-quality data asserting a positive effect of Cannabis.

### ***Clinical evidence supporting cannabis for medical conditions***

In general, there is a dearth of randomized clinical trials that compare the effect of cannabis and cannabinoids against other standard medications with clinically proven efficacy and regular use in clinical practice. When and if cannabis/cannabinoids show therapeutic effects, practitioners using evidence-based practice should not consider cannabis as a first- or second-line treatment (Martín-Sánchez, Furukawa, Taylor, & Martin, 2009). When cannabinoids have been compared to standard first-line medical treatments for pain, nausea, and cachexia, cannabinoids underperform against megestrol acetate (Timpone et al., 1997), ondansetron (Meiri et al., 2007; Söderpalm, Schuster, & de Wit, 2001), and dihydrocodeine (Frank, Serpell, Hughes, Matthews, & Kapur, 2008) and show effects comparable to tramadol and pregabalin (Rog, Nurmikko, Friede, & Young, 2005) (see Appendix B). Along with the small number of clinical trials, cannabis also carries its own set of adverse effects that must be carefully considered, monitored, and recorded (See “Adverse Effects of Cannabis” below). More important is the possibility that patients may forego effective standard medications in favor of cannabis (Abrams, 2016; Pergam et al., 2017). Therefore, the use of cannabis and cannabinoids is best considered for patients who could benefit from complementary use or when currently accepted first- and second-line medications or therapies show no or insufficient effect or demonstrate dangerous adverse events in selected patients (Aggarwal, 2016; Finnerup et al., 2015; Strouse, 2016).

From this review, as indicated in Appendix B, moderate- to high-quality evidence is available for effective treatment with cannabis for the following conditions:

- Cachexia
- Chemotherapy-induced nausea and vomiting
- Pain (resulting from cancer or rheumatoid arthritis)
- Chronic pain (resulting from fibromyalgia)
- Neuropathies (resulting from HIV/AIDS, MS, or diabetes)
- Spasticity (from MS or spinal cord injury)

However, the evidence supporting the efficacy of cannabinoids for the treatment of these conditions is limited to the populations, symptoms, formulations, dosages, and administration methods noted in Appendix B.

The literature review also identified three conditions, included in Appendix B, that are supported by a single moderate- to high-quality clinical study:

- Reduction of seizure frequency (Dravet syndrome and Lennox-Gastaut syndrome)
- Reduction of posttraumatic stress disorder (PTSD) nightmares
- Improvement in tics (Tourette syndrome)

The conditions listed above require additional study to verify the findings of the current studies. This report separates the treatment populations involved in the two epilepsy studies. The evidence for CBD as an efficacious add-on therapy is specific to the treatment groups and as such does not represent high-quality evidence for CBD as an effective treatment. The FDA is currently investigating Epidiolex, the specific formulation of CBD used in the two seizure studies, and has approved the formulation for individual Investigational New Drug exemptions (“GW’s Epidiolex® Clinical Program,” 2018).

A large number of anecdotal studies and news reports fuel interest in using cannabis for the treatment of PTSD symptoms (Gutierrez & Dubert, 2017) and severe epilepsy (“Medical Marijuana and Epilepsy,” 2017). Many states have implemented cannabis laws expressly for the treatment of epilepsy with CBD (NCSL, 2017). Despite the legislative landscape regarding CBD and epilepsy, more studies are needed to accurately assess the safety and efficacy of cannabis for the treatment of intractable seizures. The American Academy of Pediatrics (Campbell, Phillips, & Manasco, 2017) and the American Epilepsy Society (Filloux, 2015) have made similar calls for further research.

Improvements in other symptomology might be attributed to the more general effects of cannabis—sedation, appetite stimulation and euphoria. Instead of cannabis treating underlying symptoms, these three general effects of cannabis may mask symptoms and increase a subjective sense of well-being, which could improve self-reported quality of life in some patients (Fox, Bain, Glickman, Carroll, & Zajicek, 2004; Greenberg et al., 1994).

### Qualifying Conditions Without Clinical Evidence

Medical cannabis legislation includes a wide variety of qualifying conditions, some which have some scientifically supportable efficacy for symptomology, and some conditions in which there is no clinical evidence of effectiveness (see Table 4). MMP qualifying conditions are not held to the same rigor as FDA standards for safety and efficacy. The process for inclusion in a list of qualifying conditions is variable and often not dependent on the literature.

TABLE 4

### Qualifying Conditions Without Clinical Evidence

Qualifying Conditions Without Cannabis Therapeutic Clinical Evidence	Shared Symptom With an Evidence-Based Qualifying Condition
Painful peripheral neuropathy, spinal cord injury, spinal cord diseases (arachnoiditis, Tarlov cysts, hydromyelia), neurofibromatosis, chronic inflammatory demyelinating polyneuropathy, causalgia, Arnold-Chiari malformation, syringomyelia, complex regional pain syndrome, chronic radiculopathy	Neuropathy
Residual limb pain, Sjogren’s syndrome, interstitial cystitis, fibrous dysplasia, fibromyalgia, post laminectomy syndrome, sickle cell disease, arthritis, severe psoriasis, psoriatic arthritis	Pain
Intractable skeletal muscular spasticity, spastic quadriplegia, Tourette’s syndrome, spinocerebellar ataxia, muscular dystrophy, dystonia, cerebral palsy, Parkinson’s disease	Spasticity
Chronic traumatic encephalopathy, myoclonus	Seizures

Qualifying Conditions Without Cannabis Therapeutic Clinical Evidence	Shared Symptom With an Evidence-Based Qualifying Condition
	<i>(continued)</i>
Cystic fibrosis, anorexia	Wasting
Chronic pancreatitis	Nausea and vomiting
Nail-patella syndrome	Intraocular pressure (similar to glaucoma, which is not supported by quality evidence)
Huntington's disease, post-concussion syndrome, myasthenia gravis, lupus, hydrocephalus, mitochondrial disease, autism, decompensated cirrhosis, ulcerative colitis, migraine, Alzheimer's disease, amyotrophic lateral sclerosis	Diseases with multiple shared/similar symptoms

A review of all jurisdictional legislation indicates that, of the 31 jurisdictions with some legalized form of cannabis or cannabinoids, just eight cited medical studies in their statutes (Arizona, California, Delaware, Illinois, Maryland, New Hampshire, New Jersey, Rhode Island) (NCSL, 2017). The only document referenced by Illinois, Maryland, New Hampshire, New Jersey, and Rhode Island was the report published by the Institute of Medicine in 1999 (Joy, Watson, & Benson, 1999). Arizona, California, and Delaware cited one study each in addition to the Institute of Medicine report. For Arizona and Delaware, the studies were related to substance abuse (NCSL, 2017); California cited the collected works of the Center for Medicinal Cannabis Research, which was established by the state of California and is currently operating out of the University of California, San Diego (NCSL, 2017).

Grouping the current qualifying conditions by evidence is difficult. Many qualifying conditions are present in current legislation because they share symptoms with qualifying conditions that do have some scientific evidence. Table 4 highlights qualifying conditions that do not have any scientific evidence to support treatment with cannabis. Cannabis use for conditions without scientific evidence requires serious consideration on the practitioner's part, as cannabis use may exacerbate the condition's symptomology.

Qualifying conditions included in MMP statutes may be justified with human clinical evidence, preclinical animal or cellular studies, or no study at all (Madras, 2015; Maust, Bonar, Ilgen, Blow, & Kales, 2016). Practitioners must recognize and differentiate between quality human scientific evidence (Appendix B) and preclinical animal or cellular studies. For example, neurodegenerative conditions and those relating to brain trauma, which are included in some jurisdictional qualifying conditions, may be included due to animal or cellular research as well as observational studies (Mechoulam, Panikashvili, & Shohami, 2002).

No human studies have confirmed evidence for neuroprotective, anti-inflammatory, antitumoral, and antibacterial effects of cannabinoids. Some preclinical animal and cellular studies do provide evidence for those effects (Russo, 2011); however, no generalizations can be made to the human population. These studies are largely suggestive for future research.

The FDA recently issued warning letters to four companies for marketing unsubstantiated claims regarding preventing, reversing, or curing cancer; killing/inhibiting cancer cells or tumors; or other similar anticancer claims (U.S. Food & Drug Administration [FDA], November 1, 2017).

## Effects of Cannabis That May Influence Treatment Decisions

Some studies reviewed for this report are not identified as top-quality research, due to a study's multiple measures, and others because they fall outside the scope of qualifying conditions. However, several studies still reveal some medical relevance and important considerations for nurses caring for cannabis-using patients.

### Physiologic Effects of Cannabis

The treatment of certain symptomology with cannabis might be attributed to the more general and well-known effects of cannabis—sedation, appetite stimulation, and euphoria—which may contribute to a subjective sense of well-being instead of cannabis treating underlying symptoms (Joy et al., 1999). This increase in the subjective sense of well-being could improve self-reported quality of life in patients who have difficulty sleeping, chronic pain, and poor appetite (Fox et al., 2004; Wade, Makela, Robson, House, & Bateman, 2004).

A few studies have attempted to demonstrate the efficacy of these general effects as a treatment for neurodegenerative behavioral disturbances and MS sleep disturbances. For diseases that cause irritability and agitation, cannabis is suggested as a method of reducing aggressiveness in patients with inhibited mental function (i.e., Alzheimer's disease, autism, Huntington's disease) (Curtis & Rickards, 2006; Krishnan, Cairns, & Howard, 2009). However, a study of patients with dementia contradicts this claim by demonstrating that THC had no effect on objective scores of agitation, aggression, aberrant motor behavior, or other behavioral disturbances (van Den Elsen et al., 2015). It is clear that the sedative effect of cannabis is not applicable to every condition.



Studies in MS patients indicate THC use may also cause indirect behavioral benefits in the subjective improvement in quality of sleep and a reduction in sleep disturbances (Langford et al., 2013; Rog et al., 2005; Wade et al., 2004). Many of the subjective effects of cannabis are likely attributable to the associated euphoria, which can result in patients being less bothered by their symptoms, even when cannabis does not statistically ameliorate other specific symptomology. This subjective feeling of improvement and less bothersome symptoms may be highly desirable, especially in terms of compassionate care.

### **Adjunctive Use of Cannabis With Opiates, Antidepressants, and Benzodiazepines**

Among cannabis-naïve people (individuals with no or limited exposure to cannabis) who began medical cannabis, data revealed a decrease in weekly use across all medication classes, including reductions in use of opiates (-42.88%), antidepressants (-17.64%), mood stabilizers (-33.33%), and benzodiazepines (-38.89%) (Gruber et al., 2016). T-tests of this dataset indicated trends toward, but not attainment of, significant reductions in opiate and antidepressant use. A similar retrospective survey (Boehnke, Litinas, & Clauw, 2016) showed that medical cannabis use was associated with a self-reported decrease in opioid use (64% average change), decreased number and adverse effects of medications, and an improved quality of life. These results are applicable to patients on a daily regimen of multiple doses (25% use it two times, 42% use it three to four times, and 20% use it more than five times, but no dosage is given). The authors also show a reported decrease in the use of NSAIDs (from 62% to 21%), antidepressants (from 39% to 14%), and selective serotonin reuptake inhibitors (from 38% to 22%). More research is necessary to validate these correlational results.

Cannabis use is correlated with better outcomes for individuals with opioid addiction. The severity of opioid withdrawal was lower when patients used dronabinol, and this same research found a higher retention in naltrexone treatment for heroin addiction for cannabis users (Bisaga et al., 2015). A recent study showed that the legalization of medical marijuana was associated with substantial decreases in alcohol use and binge drinking among young adults (Anderson, Hansen, & Rees, 2013) and states with medical cannabis have a 24.8% lower mean annual opioid overdose mortality rate (Bachhuber, Saloner, Cunningham, & Barry, 2014). These data have spurred suggestions that cannabis may be able to serve as an exit drug and reduce the harmful use of other substances (Lucas et al., 2013; Mikuriya, 2004; Reiman, 2009). Currently, this evidence is only correlational and no studies show sufficient causal evidence for cannabis as a treatment for opioid addiction or as a substitute for opioids (Walsh et al., 2017).

### **Neurologic Symptoms**

Studies included in Appendix B demonstrate a narrow focus regarding the cannabinoid preparation administered to patients. However, the study by Wade, Robson, House, Makela, and Aram (2003) is important for its active comparison of three formulations of cannabinoid sprays (THC:CBD, THC, and CBD at 2.5mg to 120mg/day) for patients with a neurologic diagnosis. Patients included in this study presented stable symptoms that were unresponsive to standard treatments. These symptoms included neuropathic pain, spasticity, muscle spasms, impaired bladder control, and tremor. The subjective measures showed that THC spray improved scores of pain, spasm, spasm severity and frequency, and appetite; CBD spray improved pain; THC:CBD spray improved spasm severity and frequency and improved sleep. This study suggests that the various cannabinoids have differential effects on neurologic symptoms.

### **Subjective Measures vs Objective Measures for Spasticity and Pain**

Patient reports of improvement by subjective measures are the dominant type of measures used in cannabis studies (Appendix B). The Visual Analog Scale and the Numeric Rating Scale are the measurements used most often. These scales are well established and are used for clinical trials of analgesics. However, objective measures, when appropriate, are seldom used in studies. For some conditions, the focus on subjective measures can lead to possible misrepresentation of the drug's effect on symptomology (Fox et al., 2004; Joy et al., 1999).

Patients on active cannabis treatment, because of placebo effects and the euphoria elicited by cannabis, often report improvements even when no objective improvement is detected. Fox, Bain, Glickman, Carroll, & Zajicek (2004) attempted to detect objective improvement in patients with MS. In this particular study, patients took tablets of THC and the assessors used a tremor index and noted that while patients reported improvements in spasms, there was no statistical improvement on the tremor index (Fox et al., 2004).

Only one other study, carried out by Greenberg and collaborators (1994), utilized objective measures for the primary endpoint of spasticity improvement among MS patients. Patients were given a single dose of smoked cannabis (1.54% THC) and then tested on a dynamic posturographic platform. After administration, tracking errors were higher for MS patients compared to healthy volunteers, and response speed of the patients was lower. The researchers concluded that smoked cannabis worsens posture and balance in MS patients. However, "patients often had the subjective feeling that they were clinically improved, yet postural responses of both normal subjects and patients were adversely affected" (Greenberg et al., 1994).



Cooper, Comer, and Haney (2013) conducted a moderate-quality study that demonstrated significant effects of cannabis and dronabinol on pain sensitivity and tolerance—providing a different perspective on analgesia by use of cannabis. Using the cold pressor test, the researchers found that cannabis and dronabinol decreased pain sensitivity (with 3.56% THC; 20mg), increased pain tolerance (with 1.98% THC; 20mg), and decreased subjective ratings of pain intensity (with 1.98% and 3.56% THC; 20mg). Both cannabis and dronabinol significantly increased the latency to report pain, while dronabinol produced longer-lasting efficacy. The authors concluded that the comparative effects and additional benefit of more lasting efficacy signaled that dronabinol should be used over smoked cannabis. Dronabinol also elicits a significantly lower “good drug effect” (a subjective enjoyment of the drug effects) than cannabis, suggesting that dronabinol may be less likely to be abused than cannabis (Cooper, Comer, & Haney, 2013).

## **Adverse Effects of Cannabis**

Much of the information in this section is well known in the scientific literature and by health professionals (Joy et al., 1999). Although largely noncontroversial, some results cited are not conclusive and other effects are more probable than proven (Collin et al., 2010). Although preclinical studies cannot simply be translated to practice, potential risks to the patient, however tenuous, should be considered. The following is not an exhaustive list or enumeration of adverse effects but is a collection of effects self-reported during clinical studies, listed in reviews and observational studies, and reported by users.

### **Described Adverse Effects of Major Cannabinoids**

General adverse effects of THC include increased heart rate, increased appetite, sleepiness, dizziness, decreased blood pressure, dry mouth/dry eyes, decreased urination, hallucination, paranoia, anxiety, and impaired attention, memory, and psychomotor performance (FDA, 2004).

Federal limits on cannabis research prevent an adequate description of CBD-only product adverse effects. Since no large-scale studies on the adverse effects of CBD have been completed, any description of CBD adverse effects in a specific population cannot be generalized. A moderate- to high-quality study involving adults with schizophrenia and CBD use reported sedative effects (Hallak et al., 2010). In a separate study of adolescents with epilepsy using CBD, “diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests” were reported (Devinsky et al., 2017).

The adverse effects of cannabis reported by some participants across the studies in Appendix B include fatigue, nausea, asthenia, vertigo (Collin et al., 2010), and suicidal ideation (National Academies, 2017). The risk of suicide and cannabis use is a contentious area of study. Current findings are contradictory and more research is needed to confirm any association between cannabis use and suicide risk while controlling for numerous confounding variables (Walsh et al., 2017). Individuals with a greater risk of psychological disturbances and suicidal ideation should take precautions when utilizing cannabis as a therapeutic (Wilkinson, Radhakrishnan, & D’Souza, 2014).

### **Specific patient groups**

**Adolescence.** Many studies show a correlation between cannabis use and poor grades, high drop-out rates, lower income, lower percentage of college degree completion, greater need for economic assistance, unemployment, and use of other drugs (Crean, Crane, & Mason, 2011; Madras, 2015). These trends are related to recreational rather than medicinal cannabis use, but multiple confounding factors that may drive these correlations cannot be ignored in a clinical context, especially when clinicians are authorizing the use of compounds that can be abused.

- Users with persistent cannabis dependence showed greater IQ decline than those who never used cannabis. This decline is greatest in users who began using during adolescence (Meier et al., 2012). Early-onset cannabis users show greater structural differences in critical brain regions relating to memory and show a weakened ability to learn (Schuster, Hoepfner, Evins, & Gilman, 2016).
- In young (approximately age 20 and older), educated chronic users, decrements in the ability to learn and remember new information and impairment of verbal recall as well as visual recognition may occur (Schoeler, Kambeitz, Behlke, Murray, & Bhattacharyya, 2016).
- Structurally, adults who smoke cannabis regularly during adolescence have impaired neural connectivity involved in functions that require a high degree of integration (e.g., alertness and self-conscious awareness) and learning and memory (Smith et al., 2015; Yücel et al., 2008).

**Fertility.** No human studies are available; however, two preclinical studies indicate that interference with endogenous cannabinoids might increase chances of failed embryo implantation (Park, McPartland, & Glass, 2004) and cannabinoids are capable of deregulating spermatogenesis, leading to reduced fertility or infertility (Di Giacomo, De Domenico, Sette, Geremia, & Grimaldi, 2016). These same cannabinoids may even alter sperm function (du Plessis, Agarwal, & Syriac, 2015).

**Pregnancy and neonates.** The meta-analysis conducted by Gunn and colleagues (2016) indicates that exposure to cannabis in utero is associated with an increased risk of decreased birthweight and higher odds of the newborn being placed in a neonatal intensive care unit. The pooled dataset also showed a greater risk of anemia in mothers who had used cannabis during pregnancy. Only one preclinical study assessed the signaling pathways affected by prenatal THC exposure. This preclinical study shows that early exposure in utero disrupts endocannabinoid signaling and results in noticeable rewiring of mice fetal cortical circuitry (Tortoriello et al., 2014).

Presently, there are no reliable data for neurodevelopmental outcomes with early exposure to cannabis in neonatal life, through either breastfeeding or secondhand inhalation (Jaques et al., 2014; Jutras-Aswad, DiNieri, Harkany, & Hurd, 2009; Volkow, Baler, Compton, & Weiss, 2014). THC can be detected in breast milk shortly after use; however, the effects of THC in breast milk on neonatal development and neurologic function is currently unknown (Baker et al., 2018). A number of low-quality observational studies attempted to elucidate patterns of use and developmental outcomes, but their methods were imprecise or lacked longitudinal evaluation (cited in Gunn et al., 2016)

**Immunocompromised patients.** Cannabis and cannabinoid preparations (gels, tinctures, drops, sprays) can pose a serious risk to immunocompromised patients if not prepared in a sterile environment (National Academies, 2017; Thompson et al., 2017). Many jurisdictions require laboratory testing of cannabis for contaminants (Rough, 2017). The local Department of Health or MMP will provide more information on the quality-assurance practices in a specific jurisdiction.

**Dyskinesia.** It is highly likely that cannabis will exacerbate symptoms of poor balance and posture in patients with dyskinetic disorders (Greenberg et al., 1994; GW Pharmaceuticals, 2015).

**Altered cognition.** Research regarding cognitive deficits is more abundant in healthy adult participants. Insufficient evidence exists for cognitive effects in individuals with conditions that already may affect cognition (Weier & Hall, 2017). The research that does exist suggests that patients who suffer from diseases with neurologic symptomology may show greater cognitive impairment (reviewed in Walsh et al., 2017). This exacerbation of symptoms may decrease the overall effectiveness of cannabis as a therapeutic in such patients (Koppel et al., 2014). Clinical studies have shown that patients with MS who smoke cannabis at least once a month show an increase in cognitive impairment and are twice as likely to be classified as globally cognitively impaired as those who do not use cannabis (Koppel et al., 2014).

Cognitive impairment by cannabis may be dose- and age-dependent (Crean et al., 2011; Solowij & Pesa, 2012). Insufficient clinical data exist on the cognitive impairment of healthy children and adolescents.

**Mania and predisposition to mania.** There is a significant relationship between cannabis use and subsequent exacerbation and onset of bipolar disorder manic symptoms, with a roughly threefold increased risk of new onset of manic symptoms (Gibbs et al., 2015). Individuals with bipolar disorder and a cannabis use disorder also have an increased risk (odds ratio = 1.44) of suicide attempts (Carrà, Bartoli, Crocarno, Brady, & Clerici, 2014). However, these findings are not conclusive for causality.

The observed correlation of cannabis use that precedes or coincides with the manic symptoms of bipolar disorder, as well as the association between cannabis use and new-onset manic symptoms and depressive disorders, suggests a tentative causal influence of cannabis on the development of bipolar disorder symptoms (Baethge et al., 2008; Lev-Ran et al., 2014).

**Schizophrenia.** While accumulating evidence suggests a link between cannabis exposure and schizophrenia, no research exists that can conclude that cannabis use causes schizophrenia (Walsh et al., 2017). Research supports a correlation between cannabis abuse and significantly more and earlier psychotic relapses among schizophrenic patients (Linszen, Dingemans, & Lenior, 1994). The literature on cannabis and schizophrenia is scant and spread across low-quality studies and morphologic studies, but a comprehensive overview of cannabis and psychosis, schizophrenia, and schizophreniform disorder can be found in Wilkinson, Radhakrishnan, and D'Souza (2014).

Preliminary evidence suggests cannabis use is associated with an earlier age of onset for schizophrenia among predisposed male patients by an average of 2.7 years (Large, Sharma, Compton, Slade, & Niessen, 2011). Some propose that individuals predisposed to schizophrenia will experience their first schizophrenic episode earlier if cannabis is used daily in the prodromal phase (Large et al., 2011; Walsh et al., 2017). Cumulative cannabis exposure is associated with an increased rate of onset of psychosis (Kelley et al., 2016).

**Preexisting conditions.** Individuals with asthma, bronchitis, emphysema, or any pulmonary disease should not use inhaled cannabis (Hall & Solowij, 1998; Tashkin, 2013); patients with heart problems, alcohol and other drug dependence, or illnesses that may be exacerbated by cannabis use should not use cannabis (FDA, 2004). Anyone with severe diseases of the liver or kidneys should also take special precaution that the metabolic breakdown of cannabinoids does not worsen their conditions (Ishida et al., 2008; Parfieniuk & Flisiak, 2008).

In patients who suffer from seizures, high concentrations of THC may promote seizures (Katona, 2015; Rosenberg, Tsien, Whalley, & Devinsky, 2015).

Additionally, individuals with a history of suicide attempt or who are at risk for suicide and those with schizophrenia, bipolar disorder, or other psychotic condition should be informed about the risks of cannabis use and be advised to not use cannabis. Individuals with PTSD may experience distinct adverse outcomes if they also develop cannabis use disorder and should be monitored closely (Walsh et al., 2017).

#### **Overdose, abuse, dependence, and withdrawal**

**Overdose.** Cannabinoid receptors are effectively absent in the brainstem cardiorespiratory centers (Glass, Faull, & Dragunow, 1997). This is believed to preclude the possibility of a fatal overdose from cannabinoid intake. References to overdose in cannabis research relate to situations in which patients have higher than normal blood concentrations of cannabinoids, usually from overconsumption of edible THC products (Cao, Srisuma, Bronstein, & Hoyte, 2016). These increased concentrations cause prolonged and often debilitating psychoses or hyperemesis syndrome. In some cases, these adverse effects can possibly increase the risk of fatalities (Calabria, Degenhardt, Hall, & Lynskey, 2010), although overdose of cannabinoids alone has not been proven to cause fatalities.

**Induced psychosis.** Substance-induced psychosis (SIP) is characterized by hallucinations, paranoia, delusions, confusion, and disorientation (American Psychiatric Association, 2013). SIP most frequently results from the ingestion of large doses of THC, which results in SIP episodes that are typically acute and resolve relatively faster than schizophrenic psychotic episodes; therefore, SIP is not diagnostically similar to schizophrenia (Wilkinson et al., 2014).

**Cannabis use disorder.** Cannabis use disorder is defined as a problematic pattern of cannabis use leading to clinically significant impairment or distress; the clinical indications are included in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)*; American Psychiatric Association, 2013). Long-term cannabis use has the potential to lead to addiction, especially in individuals who are predisposed to addiction; approximately 9% of individuals who try cannabis are at risk for addiction (Lopez-Quintero et al., 2011). This percentage increases to roughly 16% among adult users with a history of adolescent cannabis use and to 25% to 50% among adults who use daily (Caldeira, Arria, O'Grady, Vincent, & Wish, 2008; Hall & Solowij, 1998). Cannabis users who began using in adolescence are approximately two to four times more likely to have symptoms of dependence within 2 years of their initial use when compared to users who started using cannabis as adults (Chen, Storr, & Anthony, 2009). Individuals with persistent negative emotions and psychological distress have a higher risk of abusing cannabis (Moitra, Christopher, Anderson, & Stein, 2015). The reason for this association is not clear, but Moitra, Christopher, Anderson, and Stein assert it is possible that individuals use cannabis as a method of coping with or self-medicating psychological distress. Cannabis use disorder is defined as a problematic pattern of cannabis use leading to clinically significant impairment or distress; the clinical indications are included in the *DSM-5*.

Special concern exists for individuals who use cannabis to treat symptoms of PTSD. Individuals with PTSD are three times more likely to utilize cannabis (Cogle, Bonn-Miller, Vujanovic, Zvolensky, & Hawkins, 2011) and those who develop cannabis dependence can experience heightened withdrawal symptoms, poorer cessation outcomes, and long-term reduction in the efficacy of traditional PTSD treatments (Walsh et al., 2017).

**Hyperemesis.** Cannabinoid hyperemesis syndrome is a clinical diagnosis typically seen in patients younger than age 50 with a long history of marijuana use (Lu & Agito, 2015). The presentation includes severe, cyclic nausea; vomiting; and compulsively taking extremely hot showers or baths. Other associated nonspecific symptoms are diaphoresis, bloating, abdominal discomfort, flushing, and weight loss. These symptoms are relieved with long, hot showers or baths and cessation of marijuana use (Lu & Agito, 2015).

**Cannabis withdrawal syndrome.** The average amount and duration of cannabis use required to establish dependence and withdrawal symptoms are poorly understood (Freeman & Winstock, 2015; Verweij et al., 2010). However, mild withdrawal symptoms have been reported in less than 7 days with a regimen of 20mg THC taken every 3 to 4 hours (Jones, Benowitz, & Herning, 1981). Withdrawal symptoms for cannabis include irritability, nervousness, sleeping difficulties, dysphoria, decreased appetite, restlessness, depressed mood, physical discomfort, strange and vivid dreams, craving, and anxiety (Hesse & Thylstrup, 2013). These symptoms can make cessation difficult (American Psychiatric Association, 2013).

#### **Drug-drug interactions**

Cannabinoids have the possibility of altering the metabolic breakdown of certain drugs (Stout & Cimino, 2014). Departures from normal drug metabolism can result in higher or lower than expected plasma levels, which can cause dangerous drug interactions (Lynch & Price, 2007). Information on possible interactions is available for the synthetic cannabinoids dronabinol and nabilone on the Drug Information Portal (National Institutes of Health, 2018). The interactions listed in the Drug Information Portal are not exhaustive and not directly transferable to nonsynthetic cannabinoids. However, many of the listed interactions (broadly reviewed in this section) are probable interactions, as there are not sufficient studies into cannabinoid-drug interactions. Melton (2017) provides an overview of drug interactions with cannabinoids.

Using biochemical information, Yamaori, Kushihara, Yamamoto, and Watanabe (2010) and Yamaori, Ebisawa, Okushima, Yamamoto, and Watanabe (2011) determined that cannabinoids, particularly CBD, competitively inhibit cytochrome P450 (CYP450) isoforms. This interaction could result in dangerous interactions with levodopa, sildenafil, fentanyl, and other drugs metabolized by CYP3A enzymes (specifically, CYP3A4, CYP3A5, and CYP3A7) as well as CYP1 enzymes (Yamaori et al., 2010; Yamaori et al., 2011).

THC also inhibits CYP1 enzymes in a competitive manner (Ogu & Maxa, 2000; Zanger & Schwab, 2013). Ogu and Maxa found that CBN, a metabolite of THC, is an effective inhibitor of CYP1A2 and CYP1B1. The authors warn that inhibition of CYP1 enzymes could result in drug interactions with caffeine, clozapine, warfarin, and other drugs. One of the high-quality studies in Appendix B lists specific concerns for concomitant use of CBD with common antiepileptic drugs. CBD increases concentrations of the active metabolite of clobazam through inhibition of CYP2C19, which likely caused some adverse effects in the study population (Thiele et al., 2018). The same authors noted an increase in transaminase levels in patients using CBD and valproate (Thiele et al., 2018).

THC, CBD, and CBN are all present in raw cannabis. Pyrolysis (high temperature heating) is often required to create substantial amounts of the active cannabinoids THC and CBD, but endogenous enzymes are capable of forming active cannabinoids in stored cannabis (Mechoulam & Burstein, 1973). Many formulations of synthetic and isolated cannabinoids contain THC, CBD, or a combination of the two. Drugs that contain THC and synthetic analogues include dronabinol, nabilone, and nabiximols. CBD is present in nabiximols and Epidiolex. CBN and other cannabinoids may or may not be present in cannabis extracts, depending on manufacturer specifications and specific production methods (Omar, Olivares, Alzaga, & Etxebarria, 2013; Webster & Sarna, 2002).

Nurses must be aware that nonpharmaceutical preparations (including, but not limited to, tinctures, edibles, and raw cannabis) may contain any or none of the cannabinoids listed in this section. Whenever possible, patients should use products with laboratory-confirmed and listed concentrations of cannabinoids.

## Methods of Administration

While patients may choose to use any of the following methods of administration, note that the amount of cannabis, onset, and total impact of the effects will vary with each method of administration. In addition, no randomized control studies have sufficiently compared drug activity based on the administration method.

The studies listed in Appendix B show that the most studied methods of administering medical cannabis are smoking and oromucosal sprays. Insufficient evidence exists for vaporized cannabis, edibles, dabbing (superheated vaporization of oils or waxy extracts of cannabis), and other routes of delivery. However, the FDA-approved cannabinoids (dronabinol and nabilone) are administered orally or by an oromucosal route.

Oral administration has delayed effects (Grotenhermen, 2003). Additionally, there is inconsistent absorption into the bloodstream because cannabinoids are hydrophobic. This effect may have benefits for patients wishing to control symptoms over a longer period of time than what can be achieved with a comparable dose via inhalation and oromucosal delivery (Grotenhermen, 2003).

Sublingual and mucosal sprays have a benefit of directly accessing the bloodstream; as a result, oromucosal doses have less dosage variability than smoked cannabis and edibles, but are limited by slower absorption and lower rate of THC delivery to the brain (Karschner et al., 2011). This means that oromucosal routes may be less effective for conditions that require high doses of THC to alleviate chronic symptoms with rapid acute onset.

Smoked and vaporized cannabis has the advantage of rapid absorption into the bloodstream (Grotenhermen, 2003). Vaporization creates fewer pyrolytic compounds that irritate respiratory tissue (Hazekamp, Ruhaak, Zuurman, van Gerven, & Verpoorte, 2006). However, both methods show significant loss of active compounds, with 40% to 46% of THC lost to combustion and an average 35% of THC directly exhaled (Hazekamp et al., 2006; Herning, Hooker, & Jones, 1986).

Butane honey oil (or other oils used for dabbing) (Stockburger, 2016), hashish, and other extracted resins often carry solvent impurities, especially when manufactured by nonprofessionals. Dabbing is a method of superheating small concentrations of cannabis resins on a small metal heating element to produce a vapor for inhalation. Combustion of these products is likely to deliver "significant amounts of toxic degradation products" and these concerns are extended to e-cigarettes that use a similar heating element (Meehan-Atrash, Luo, & Strongin, 2017). These administration methods and formulations should not be considered for medical applications (Stockburger, 2016).

The use of suppositories, injection, transdermal patches, and topical application for the administration of cannabis extracts and cannabinoids has not been studied in a clinical setting (Grotenhermen, 2003).



## Dosing Considerations

The only FDA-approved dosing guidelines for cannabinoids are for the drugs dronabinol and nabilone. These two formulations are synthetically derived THC. A consistent trend in dosage can be seen across studies (Appendix B). Dosages start at 2.5mg, with 15mg THC established as effective for chemotherapy-induced nausea. Dosages between 2.5mg and 10mg typically show tolerable adverse effects, such as dry mouth and psychoactivity (Whiting et al., 2015). FDA-approved nabilone and dronabinol are the only cannabinoids available through prescription, which can be dispensed through a pharmacist and may be covered by some insurance providers. The FDA provides information about dosages, indications, and interactions of these drugs on their Dockets Management website (FDA, 2004, 2006, August 2017).

Since cannabis cannot be prescribed and therefore authorizing practitioners cannot provide the patient with a specific dosage, dosing schedule, or recommended delivery method, many health care practitioners feel unprepared to educate patients, resulting in practitioners deferring to dispensary staff as the cannabis subject experts (Kondrad & Reid, 2013; Rubin, 2017). It is the patient who will decide on which dispensary to utilize, and the specifics of administration, formulations, and dosages will be available at licensed dispensaries. However, dispensaries vary widely in their product quality, laboratory testing, proper and accurate product labeling, and employee expertise (Haug et al., 2016; Vandrey et al., 2015). A recent analysis of 31 companies selling CBD products found that only about 31% of products were accurately labeled (Bonn-Miller et al., 2017). This same survey found that approximately 21% of products had nonnegligible amounts of other cannabinoids, including THC.

A recent survey showed that self-titration by the patient to the desired effect is the most common strategy for dosing (Hazekamp, Ware, Muller-Vahl, Abrams, & Grotenhermen, 2013). Kowal, Hazekamp, and Grotenhermen (2016) note that because of the large variation in patient responses to cannabis, patients will need to understand they must titrate their personal dosage and establish the minimum efficacious dose and a stable schedule over 1 to 2 weeks. Continual assessment of perceived efficacy and adverse effects is recommended. Full effects should be seen within 2 weeks; if there is no improvement of symptomatology within an additional 2 weeks, consideration of cessation is suggested. If adverse effects become problematic, cessation is warranted. A dosage diary, maintained by the patient or caregiver, can be helpful to keep track of dosages, administration methods, formulations, and scheduling.

As suggested in this report, numerous factors may alter the physiologic effects of cannabis in any given patient. Important considerations for usage and amount include the individual's age, health history, prior experience with cannabis, concurrent medications, the product's cannabinoid concentrations, method of administration, and timing of doses.

Typically, jurisdictions require renewal of medical marijuana registration every year (NCSL, 2017). Some also require certifying practitioners to register with the MMP annually (NCSL, 2017). Details about renewals are provided by the jurisdiction's Department of Health and/or MMP.

## The Entourage Effect

The entourage effect is a frequently mentioned attribute of cannabis. The phrase refers to the large number of cannabinoids, flavonoids, and other compounds (such as terpenes/terpenoids, phenols, etc.) present in cannabis that show similar and possible synergistic effects (Russo, 2011).

Working under the assumption that the whole plant is greater than the sum of its parts, cannabis growers have been crossing plants to develop chemovars (chemical variations) that have differential effects. Different varieties are purported to be more "uplifting," or "relaxing" or increase appetite. Some dispensaries have begun listing and advertising various cannabinoid ratios and providing detailed terpene profiles in certain strains and products (Chen, 2017).

Despite advertising, no experimental study has investigated the claim of synergistic effects beyond preliminary work on THC:CBD formulations (Gupta, 2014). Since no clinical research has substantiated the entourage effect, this report cannot explicitly state that terpenes and other constituent compounds in cannabis in any way affect the therapeutic potential of cannabis (Health Canada, 2013).

## Price Consideration

Across all the studies included in this report, beneficial effects of cannabis can only be derived from frequent and continued doses, which may be prohibitively expensive. In the Framework for Legalization in Canada (Health Canada, 2016), the authors noted that "[m]any patients cited the high costs they incur today in purchasing cannabis from licensed producers. . . . it is not uncommon for patients to spend hundreds or thousands of dollars each month in order to acquire a sufficient supply of cannabis." Study participants using nabilone at a 2mg daily dose could expect to pay over \$4,000 (Canadian) for an annual supply in Canada. A list of the average cost of cannabinoids and whole cannabis is provided in Table 5.

TABLE 5

**Cost of Cannabinoids (U.S. Dollars)\***

Drug Name	Price Averages
Sativex	A vial with 15 sprays costs \$22 dollars/vial. Average dose of 5 sprays per day yields \$7/day and \$51/week. This price was derived from the 2005 Patented Medicine Prices Review Board of Canada ( <a href="http://www.pm-prb-cepmb.gc.ca">www.pm-prb-cepmb.gc.ca</a> ) report on Sativex. <i>Available in Canada. Not available in the United States (undergoing FDA Fast Track trials).</i>
Cesamet (nabilone) Schedule II Controlled Substance	~\$2,000 for 50/1-mg capsules. Wide variance in effective dose per day (2mg to 10mg). Average dose of 2mg/day yields \$80/day. <i>FDA approved. Not covered by Medicare.</i>
Marinol (dronabinol) Schedule III Controlled Substance	\$140–\$271.05 for 60/2.5-mg capsules, \$150–\$281.95 for 30/5-mg capsules, \$500–\$1,019.40 for 60/10-mg capsules. Average dose of 5mg–10mg/day yields \$8–\$16/day without insurance. <i>FDA approved. Covered by Medicare. Insurance may cover 3%–99% of costs.</i>
Medical cannabis	~\$150–\$200 for 28g as the low end of possible dispensary prices in the United States. (Colorado Department of Revenue, 2015; Hickey, 2014; “Is it Cheaper to Buy,” 2016) A starting dose of 5% THC per cannabis cigarette and the goal of 2.5mg absorbed THC requires 0.60g–1g of cannabis per dose. For pain, this may require four or more doses per day. This regimen could result in \$600/month for management of pain using smoked cannabis. Patient cultivation regulations may reduce this cost. (This price estimate is approximate for all products sold at U.S. medical dispensaries.)

\*Price ranges collated from [www.goodrx.com](http://www.goodrx.com), [www.webmd.com](http://www.webmd.com), and [www.wellrx.com](http://www.wellrx.com)

**Nursing Implications**

Nurses need practical information to care for the increasing number of patients who utilize cannabis via an MMP as well as the larger population who self-administer cannabis as a treatment for various symptomatology or for recreational purposes. As noted previously, evidence for cannabis use in described conditions is limited by inadequate study and limited legal availability of cannabis for research purposes. Statutory authorization of cannabis use for certain conditions has been influenced by advocacy; as a result, some qualifying conditions are present in statutes without evidence of their effect. Regardless of existing evidence, individuals are using cannabis and nurses will care for these patients. The studies and literature in this report should inform nursing practice that represents the best interests of the patient.

**Six Principles of Essential Knowledge**

1. *The nurse shall have a working knowledge of the current state of legalization of medical and recreational cannabis use.*

Critical to the care of patients who use cannabis is a working knowledge of the current state of legalization of medical and recreational cannabis use. Knowledge of the federal government prohibitions and any guidance from the federal government allows the nurse to be well informed regarding potential questions about the legality of the use of cannabis as a medical treatment.

Although the use of marijuana pursuant to authorized MMPs conflicts with federal law and regulations, at present there is no controlling case law holding that Congress intended to preempt the field of regulation of cannabis use under its supremacy powers (*Beck v. City of Wyoming*, 2014; Mikos, 2012).

2. *The nurse shall have a working knowledge of the jurisdiction's MMP.*

Rules and statutes for the MMP include specific information for the particular jurisdiction. Each jurisdiction has widely different laws, rules, and regulations regarding medical cannabis. The jurisdiction's MMP or Department of Health will provide the specific details in each jurisdiction (NCSL, 2017). The laws regarding the MMPs are frequently changing. Safe nursing practice includes an awareness of any regulatory changes that may affect their practice.

Usually, a medication is prescribed with a specific dose, route, and frequency. A health care provider, however, cannot prescribe medical cannabis; the provider certifies that the patient has a state qualifying condition. Several jurisdictions identify an APRN as one of the health care providers who can certify that a patient has a qualifying condition. Access to medical cannabis can only be obtained once the patient visits a state-authorized cannabis dispensary with a valid registration to the MMP. The nature of the certification process is different from any other substance recommended to a patient by a health care provider. An MMP's certification process presents a special set of implications (NCSL, 2017). A medical certification is not required for FDA-approved cannabinoids (dronabinol and nabilone) and these medications may be prescribed without registration with an MMP.

Health care practitioners who certify that a patient has a qualifying condition need to consider all aspects of the patient's history, diagnostic information, and mitigating concerns. Precautions should be taken in the consideration of, and decision to cer-



tify, patients with a medical cannabis qualifying condition. Since cannabis is a known substance of abuse, sufficient consideration for the potential for addiction must be included in the assessment process. Other safe practice considerations include certification for patients who show a resistance to conventional treatments or for those who may benefit from cannabis as an adjunctive, and continued monitoring of the patient after certification and treatment with cannabis.

Additionally, because medical cannabis is not covered by insurance or Medicare, use of medical cannabis may impose a significant financial burden on the patient and due consideration must be given to this potential impact.

Patients that utilize MMPs are frequently debilitated by their condition. Cannabis is most often not delivered by the traditional pill route. For some patients, delivery and administration of cannabis may be an unfamiliar and complicated process that is not possible for the debilitated patient to perform. Therefore, state law and rules may also provide for administration by designated caregivers (i.e., those specifically authorized to assist with the patient's medical use of cannabis). A few states allow an employee of a hospice provider or nursing or medical facility or a visiting nurse, personal care attendant, or home health aide to assist in the qualifying patient's medical use of cannabis (including, but not limited to, California, Massachusetts, Minnesota, and New Hampshire) (NCSL, 2017). These designated caregivers must generally be registered with the state and meet the qualifications and limits of the caregiving statute.

**3. *The nurse shall have an understanding of the endocannabinoid system, cannabinoid receptors, cannabinoids, and the interactions between them.***

The endocannabinoid system consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids (Mackie, 2008). Discovered in 1973, this system includes a series of cannabinoid receptors throughout the body embedded in cell membranes thought to promote homeostasis. Endocannabinoids are naturally occurring substances within the body, while phytocannabinoids (plant substances that stimulate cannabinoid receptors) are found in cannabis. The most well known of these cannabinoids is THC; however CBD and CBN are gaining interest in therapeutic use (Pacher et al., 2006).

**4. *The nurse shall have an understanding of cannabis pharmacology and the research associated with the medical use of cannabis.***

Research related to cannabis use in humans is limited due to government restrictions on research involving cannabis. Therefore, information regarding medicinal use of cannabis must be derived from credible research using randomized placebo-controlled studies. These particular studies are the most likely to elucidate causality in treatments and are the only trusted source of evidence for cannabis as a clinical intervention.

Present available scientific evidence exists for the use of cannabis in specific qualifying conditions. Moderate- to high-quality evidence exists for the following:

- Cachexia
- Chemotherapy-induced nausea and vomiting
- Pain (resulting from cancer or rheumatoid arthritis)
- Chronic pain (resulting from fibromyalgia),
- Neuropathies (resulting from HIV/AIDS, MS, or diabetes)
- Spasticity (from MS or spinal cord injury)

Other important considerations are the adverse effects of cannabis, specifically the risks to various patient groups; concerns regarding abuse, dependence, overdose, and withdrawal; and drug-to-drug interactions.

Most cannabis preparations are not included in FDA drug resources (except nabilone and dronabinol). Patients do not receive a prescription for medical cannabis noting the route and dosage. Nurses must be aware of the general information regarding various methods of administration and the principles of self-titration dosing. The state-authorized cannabis dispensary often gives the patient advice regarding route and dosage, following the self-titration method of dosing.

**5. *The nurse shall be able to identify the safety considerations for patient use of cannabis.***

Administration of medical cannabis can only be carried out by the certified patient, or the designated caregivers registered to care for the patient according to the MMP. Health care professionals may administer medical cannabis according to the MMP and facility policy (NCSL, 2017).

Storage considerations include keeping cannabis out of the reach of children, minors, and nonregistered individuals; storing all cannabis products in a locked area; keeping cannabis in the child-resistant packaging from the store; and storing raw cannabis in a cool, dry, place.

Disposal of unused cannabis products should be completed according to the DEA's Disposal Act (DEA, 2014). Generally, one can locate a collection receptacle via the DEA Registration Call Center (800-882-9539).

**6. *The nurse shall approach the patient without judgment regarding the patient's choice of treatment or preferences in managing pain and other distressing symptoms.***

The care of patients by nurses in any capacity is grounded in ethical practice, that is, the moral principles that guide one's conduct. Beneficence, nonmaleficence, autonomy, fairness, and loyalty are some of the more common moral principles that guide one's conduct. In addition to personal ethics, nurses are also guided by standards of practice, which are based on professional values, and/or a code of ethics. Awareness of one's own beliefs and attitudes about any therapeutic intervention is vital, as nurses are expected to provide patient care without personal judgment of patients.

Although medical cannabis legislation is evolving and more jurisdictions are adopting MMPs, social acceptance may not be evolving at the same pace. In addition, scientific evidence for cannabis use exists for some but not all conditions. The evolution of legislation, social acceptance, and scientific evidence creates ethically challenging patient care situations. Ethical decision making regarding a patient's care must include the patient as well as the family, caregivers, and other practitioners involved in the patient's care.

Necessary ethical considerations regarding a patient's treatment with cannabis include, but are not limited to:

- Clinical indications, such as diagnosis, history, goals for use of medical marijuana, probability of success, other options for care
- Patient's personal preferences based on information of benefits and risks
- Attention to decision making by the patient's proxy, parent, or guardian, if the patient is incapacitated in decision making or is a minor
- Quality of life based on the patient's subjective viewpoint
- Situational context, such as family and other important relationships, economic factors, access to care, and potential harm to others.

## **Conclusion**

Available moderate- to high-quality research, along with state and federal laws regarding the use of cannabis, is a necessary component of knowledge in the nursing care of a patient using cannabis. Without the usual FDA approval of cannabis that identifies precise indications, dosage, and efficacy for medications, nurses must have a much more nuanced knowledge while caring for the patient using cannabis. The six principles of essential knowledge listed above create a strong foundation for safe and knowledgeable nursing care of patients using medical or recreational cannabis.

These principles are the foundation for the NCSBN National Nursing Guidelines for Medical Marijuana that follow in Part II of this report:

- Nursing Care of the Patient Using Medical Marijuana
- Medical Marijuana Education in Pre-Licensure Nursing Programs
- Medical Marijuana Education in APRN Nursing Programs
- APRN Certifying a Medical Marijuana Qualifying Condition.

## **References**

See Appendix C for Part I references.

# The NCSBN National Nursing Guidelines for Medical Marijuana

Nursing Care of the Patient Using Medical Marijuana

Medical Marijuana Education in Pre-Licensure Nursing Programs

Medical Marijuana Education in APRN Nursing Programs

APRNs Certifying a Medical Marijuana Qualifying Condition

# Nursing Care of the Patient Using Medical Marijuana

## Purpose of the Guidelines

Over 31 US jurisdictions (including the District of Columbia), Guam, and Puerto Rico passed legislation legalizing cannabis for medical use. Several other jurisdictions also have legalized cannabis for medical use.\* Each medical marijuana program has unique characteristics. In the United States, cannabis is a Schedule I Controlled Substance. Therefore, medical cannabis is unlike most other therapeutics in that providers cannot prescribe cannabis, nor can pharmacies dispense cannabis. However, applicable jurisdiction statutes and rules provide for the manufacture, distribution, and use of cannabis for medical purposes.

These guidelines provide nurses with principles of safe and knowledgeable practice to promote patient safety when caring for patients using medical marijuana.

## Definitions

*Cannabis.* Any raw preparation of the leaves or flowers from the plant genus *Cannabis*. This report uses “cannabis” as a shorthand that also includes cannabinoids.

*Cannabidiol (CBD).* A major cannabinoid that indirectly antagonizes cannabinoid receptors, which may attenuate the psychoactive effects of tetrahydrocannabinol.

*Cannabinoid.* Any chemical compound that acts on cannabinoid receptors. These include endogenous and exogenous cannabinoids.

*Cannabinol (CBN).* A cannabinoid more commonly found in aged cannabis as a metabolite of other cannabinoids. It is nonpsychoactive.

*Certify.* The act of confirming that a patient has a qualifying condition. Many jurisdictions use alternative phrases such as “attest” or “authorize”; however, 13 of 29 jurisdictions use “certify” language in their statutes.

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\* In Australia, cannabis for medical use is federally legal, with states allowed to implement as they see fit. Although Bermuda has not legislated use of marijuana, their Supreme Court ruled that citizens could apply for personal licenses to possess cannabis for medical use. Cannabis for medical use is federally legal in all provinces of Canada. In New Zealand, physicians may prescribe CBD and cannabis-based products.

*Clinical research.* An activity that involves studies that experimentally assign randomized human participants to one or more drug interventions to evaluate the effects on health outcomes

*Designated caregiver.* An individual who is selected by the Medical Marijuana Program qualifying patient and authorized by the Medical Marijuana Program to purchase and/or administer cannabis on the patient’s behalf. Also sometimes referred to as an “alternate caregiver.”

*Dronabinol.* The generic name for synthetic tetrahydrocannabinol. It is the active ingredient in the U.S. Food & Drug Administration–approved drug Marinol.

*Endocannabinoid system.* A system that consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids.

*Marijuana.* A cultivated cannabis plant, whether for recreational or medicinal use. The words “marijuana” and “cannabis” are often used interchangeably in various lay and scientific literature. These guidelines will primarily use the word “cannabis.” When referring to a medical marijuana program, the guidelines will use the word “marijuana,” as it is often used within program references.

*Medical Marijuana Program (MMP).* The official jurisdictional resource for the use of cannabis for medical purposes. Search the jurisdiction’s website or Department of Health for “medical cannabis program” or “medical marijuana program.”<sup>1</sup>

*Nabilone.* The generic name for a synthetic cannabinoid similar to tetrahydrocannabinol. It is the active ingredient in the U.S. Food & Drug Administration–approved drug Cesamet.

*Schedule I Controlled Substance.* Defined in the federal Controlled Substances Act<sup>2</sup> as those substances that have a high potential for abuse; no currently accepted medical use in treatment in the United States; and a lack of accepted safety for use of the substance under medical supervision.

*Tetrahydrocannabinol (THC).* One of many cannabinoids found in cannabis. THC is the primary substance responsible for most of the characteristic psychoactive effects of cannabis.<sup>3</sup>

## Recommendations

### Essential Knowledge

1. The nurse shall have a working knowledge of the current state of legalization of medical and recreational cannabis use.
  - *The Drug Enforcement Agency (DEA) classifies cannabis as a Schedule I Controlled Substance. This classification not only prohibits practitioners from prescribing cannabis, it also prohibits most research using cannabis.*<sup>4</sup>
  - *The process for obtaining cannabis for federally funded research purposes is cumbersome. Currently, the only legal source of cannabis for research purposes is grown in limited quantities at the University of Mississippi.*<sup>5</sup> *The DEA sets an annual quota for cannabis grown for research purposes.*<sup>6</sup>
  - *Over 31 jurisdictions (including the District of Columbia), Guam, and Puerto Rico passed legislation legalizing cannabis for medical purposes. In these laws, the jurisdiction has adopted exemptions legalizing the use of cannabis for medical purposes. Although the use of marijuana pursuant to authorized MMPs conflicts with federal law and regulations, at present there is no controlling case law holding that Congress intended to preempt the field of regulation of cannabis use under its supremacy powers.*<sup>7</sup>
  - *An increasing proportion of jurisdictions have also decriminalized or legalized recreational cannabis use.*<sup>8</sup>
  - *The federal government's position on prosecuting the use of cannabis that is legal under applicable jurisdiction law has been set out in U.S. Department of Justice position papers. In 2009, the U.S. Attorney General took a position that discourages federal prosecutors from prosecuting people who distribute or use cannabis for medical purposes in compliance with applicable jurisdiction law; further similar guidance was given in 2011, 2013, and 2014.*<sup>9</sup> *In January 2018, the U.S. Office of the Attorney General rescinded the previous nationwide guidance specific to marijuana enforcement. The 2018 memorandum*<sup>10</sup> *provides that federal prosecutors follow the well-established principles in deciding which cases to prosecute, namely, the prosecution is to weigh all relevant considerations, including priorities set by the attorneys general, seriousness of the crime, deterrent effect of criminal prosecution, and cumulative impact of particular crimes on the community.*
2. The nurse shall have general knowledge of the principles of an MMP.
  - *MMPs are defined and described within the statute and rules of the specific jurisdiction. The relevant statute or rules are most easily located through the jurisdiction's Department of Health and MMP.*<sup>11</sup> *Laws and rules regarding MMPs are an evolving process. Always confirm use of the most recent versions.*
  - *A health care provider does not prescribe cannabis.*
  - *The MMP will specify the qualifying conditions and the certifying process as well as the type of health care provider who can certify a qualifying condition.*<sup>12</sup>
  - *The MMP will specify whether an advanced practice registered nurse can certify a qualifying condition and whether a specific course or training is required in order to participate in certifying an MMP qualifying condition.*<sup>13</sup>
3. The nurse shall have a general understanding of the endocannabinoid system, cannabinoid receptors, cannabinoids, and the interactions between them.
  - *The endocannabinoid system consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids.*<sup>16</sup>
  - *Discovered in 1973, this system includes a series of cannabinoid receptors throughout the body embedded in cell membranes that, when stimulated by endocannabinoids, are thought to promote homeostasis.*<sup>17</sup>
  - *Endocannabinoids are naturally occurring substances within the body, while phytocannabinoids (plant substances that stimulate cannabinoid receptors) are found in cannabis.*<sup>18</sup>
  - *The most well known of these cannabinoids is tetrahydrocannabinol (THC); however, cannabidiol (CBD) and cannabinol (CBN) are gaining interest in therapeutic use.*<sup>19</sup>
4. The nurse shall have an understanding of cannabis pharmacology and the research associated with the medical use of cannabis.

*Due to government restrictions on research involving cannabis, the surge of legislation has outpaced research, leaving nurses with few resources when caring for patients who use medical cannabis. Therefore, information regarding medicinal use of cannabis must be derived from moderate- to high-quality evidence using randomized placebo-controlled studies. These particular studies are the most likely to elucidate causality in treatments and are the only trusted source of evidence for cannabis as a clinical intervention. Research on cannabis is an evolving body of work. As with any scientific literature, it is important to rely on the most recent high-quality evidence.*

  - a. Current scientific evidence exists for the use of cannabis for the following qualifying conditions
    - *Moderate- to high-quality evidence exists for*
      - *cachexia*
      - *chemotherapy-induced nausea and vomiting*
      - *pain (resulting from cancer or rheumatoid arthritis)*
      - *chronic pain (resulting from fibromyalgia),*
      - *neuropathies (resulting from HIV/AIDS, Multiple Sclerosis {MS}, or diabetes)*







3. The nurse shall be able to identify the safety considerations for patient use of cannabis.
  - *Administration of cannabis for medical use can only be carried out by the certified patient or designated caregivers registered to care for the patient.*
  - *Cannabis storage considerations include:*
    - *keeping cannabis out of the reach of children, minors, and non-registered individuals*
    - *storing all cannabis products in a locked area*
    - *keeping cannabis in the original child-resistant packaging*
    - *storing raw cannabis in a cool, dry, place*
    - *following labeling guidelines for storage and expiration dates*
  - *Disposal of unused cannabis products should be completed according to the DEA's Disposal Act.<sup>41</sup> Generally, one can locate a collection receptacle via the DEA Registration Call Center (800-882-9539).*

### Medical Marijuana Administration Considerations

1. A nurse shall not administer cannabis to a patient unless specifically authorized by jurisdiction law.<sup>42</sup>
2. Instances in which the nurse may administer cannabis or synthetic THC to a patient.
  - *Administration of FDA-approved synthetic THC drugs (dronabinol and nabilone) as per facility formulary and policy*
  - *As a registered MMP-designated caregiver*
    - *The majority of jurisdictions allow a designated caregiver to assist a patient with the medical use of cannabis.*
    - *These caregivers must meet specific qualifications and be registered with the MMP and must not practice outside of the limits of the caregiving statute.<sup>43</sup>*
    - *Some jurisdictions allow an employee of a hospice provider or nursing or medical facility, or a visiting nurse, to assist in the administration of medical marijuana.*
    - *Check the most current MMP statute or rules.<sup>44</sup>*
    - *Check facility policy regarding medical marijuana administration.*

### Ethical Considerations

In addition to ethical responsibilities under the nurse's jurisdictional law, the nurse shall approach the patient without judgment regarding the patient's choice of treatment or preferences in managing pain and other distressing symptoms.

*Awareness of one's own beliefs and attitudes about any therapeutic intervention is vital, as nurses are expected to provide patient care without personal judgment of patients.*

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# Medical Marijuana Education in Pre-Licensure Nursing Programs

## Purpose of the Guidelines

Over 31 US jurisdictions (including the District of Columbia), Guam, and Puerto Rico passed legislation legalizing cannabis for medical use. Several other jurisdictions also have legalized cannabis for medical use.\* Each medical marijuana program has unique characteristics. In the United States, cannabis is a Schedule I Controlled Substance. Therefore, medical cannabis is unlike most other therapeutics in that providers cannot prescribe cannabis, nor can pharmacies dispense cannabis. However, applicable jurisdiction statutes and rules provide for the manufacture, distribution, and use of cannabis for medical purposes.

These recommendations for curriculum content provide nurses with principles of safe and knowledgeable practice to promote patient safety when caring for patients using medical marijuana.

## Definitions

*Cannabis.* Any raw preparation of the leaves or flowers from the plant genus *Cannabis*. This report uses “cannabis” as a shorthand that also includes cannabinoids.

*Cannabidiol (CBD).* A major cannabinoid that indirectly antagonizes cannabinoid receptors, which may attenuate the psychoactive effects of tetrahydrocannabinol.

*Cannabinoid.* Any chemical compound that acts on cannabinoid receptors. These include endogenous and exogenous cannabinoids.

*Cannabinol (CBN).* A cannabinoid more commonly found in aged cannabis as a metabolite of other cannabinoids. It is nonpsychoactive.

*Certify.* The act of confirming that a patient has a qualifying condition. Many jurisdictions use alternative phrases such as “attest”

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\* In Australia, cannabis for medical use is federally legal, with states allowed to implement as they see fit. Although Bermuda has not legislated use of marijuana, their Supreme Court ruled that citizens could apply for personal licenses to possess cannabis for medical use. Cannabis for medical use is federally legal in all provinces of Canada. In New Zealand, physicians may prescribe CBD and cannabis-based products.

or “authorize”; however, 13 of 29 jurisdictions use “certify” language in their statutes.

*Clinical research.* An activity that involves studies that experimentally assign randomized human participants to one or more drug interventions to evaluate the effects on health outcomes

*Designated caregiver.* An individual who is selected by the Medical Marijuana Program qualifying patient and authorized by the Medical Marijuana Program to purchase and/or administer cannabis on the patient’s behalf. Also sometimes referred to as an “alternate caregiver.”

*Dronabinol.* The generic name for synthetic tetrahydrocannabinol. It is the active ingredient in the U.S. Food & Drug Administration–approved drug Marinol.

*Endocannabinoid system.* A system that consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids.

*Marijuana.* A cultivated cannabis plant, whether for recreational or medicinal use. The words “marijuana” and “cannabis” are often used interchangeably in various lay and scientific literature. These guidelines will primarily use the word “cannabis.” When referring to a medical marijuana program, the guidelines will use the word “marijuana,” as it is often used within program references.

*Medical Marijuana Program (MMP).* The official jurisdictional resource for the use of cannabis for medical purposes. Search the jurisdiction’s website or Department of Health for “medical cannabis program” or “medical marijuana program.”<sup>1</sup>

*Nabilone.* The generic name for a synthetic cannabinoid similar to tetrahydrocannabinol. It is the active ingredient in the U.S. Food & Drug Administration–approved drug Cesamet.

*Schedule I Controlled Substance.* Defined in the federal Controlled Substances Act<sup>2</sup> as those substances that have a high potential for abuse; no currently accepted medical use in treatment in the United States; and a lack of accepted safety for use of the substance under medical supervision.

*Tetrahydrocannabinol (THC).* One of many cannabinoids found in cannabis. THC is the primary substance responsible for most of the characteristic psychoactive effects of cannabis.<sup>3</sup>



## Recommendations

1. The nursing student shall have a working knowledge of the current state of legalization of medical and recreational cannabis use.
  - *The Drug Enforcement Agency (DEA) classifies cannabis as a Schedule I Controlled Substance. This classification not only prohibits practitioners from prescribing cannabis, it also prohibits most research using cannabis.*<sup>4</sup>
  - *The process for obtaining cannabis for federally funded research purposes is cumbersome. Currently, the only legal source of cannabis for research purposes is grown in limited quantities at the University of Mississippi.*<sup>5</sup> *The DEA sets an annual quota for cannabis grown for research purposes.*<sup>6</sup>
  - *Over 31 jurisdictions (including the District of Columbia), Guam, and Puerto Rico passed legislation legalizing cannabis for medical purposes. In these laws, the jurisdiction has adopted exemptions legalizing the use of cannabis for medical purposes. Although the use of marijuana pursuant to authorized MMPs conflicts with federal law and regulations, at present there is no controlling case law holding that Congress intended to preempt the field of regulation of cannabis use under its supremacy powers.*<sup>7</sup>
  - *An increasing proportion of jurisdictions have also decriminalized or legalized recreational cannabis use.*<sup>8</sup>
  - *The federal government's position on prosecuting the use of cannabis that is legal under applicable jurisdiction law has been set out in U.S. Department of Justice position papers. In 2009, the U.S. Attorney General took a position that discourages federal prosecutors from prosecuting people who distribute or use cannabis for medical purposes in compliance with applicable jurisdiction law; further similar guidance was given in 2011, 2013, and 2014.*<sup>9</sup> *In January 2018, the U.S. Office of the Attorney General rescinded the previous nationwide guidance specific to marijuana enforcement. The 2018 memorandum*<sup>10</sup> *provides that federal prosecutors follow the well-established principles in deciding which cases to prosecute, namely, the prosecution is to weigh all relevant considerations, including priorities set by the attorneys general, seriousness of the crime, deterrent effect of criminal prosecution, and cumulative impact of particular crimes on the community.*
2. The nursing student shall have general knowledge of the principles of an MMP.
  - *MMPs are defined and described within the statute and rules of the specific jurisdiction. The relevant statute or rules are most easily located through the jurisdiction's Department of Health and MMP.*<sup>11</sup> *Laws and rules regarding MMPs are an evolving process. Always confirm use of the most recent versions.*
  - *A health care provider does not prescribe cannabis.*
  - *The MMP will specify the qualifying conditions and the certifying process as well as the type of health care provider who can certify a qualifying condition.*<sup>12</sup>
  - *The MMP will specify whether an APRN can certify a qualifying condition and whether a specific course or training is required in order to participate in certifying an MMP qualifying condition.*<sup>13</sup>
3. The nursing student shall have a general understanding of the endocannabinoid system, cannabinoid receptors, cannabinoids, and the interactions between them.
  - *After the qualifying condition is certified, the patient registers with the MMP. Once registered, the patient can obtain cannabis from a jurisdiction-authorized cannabis dispensary.*
  - *Procurement and administration of cannabis for medical purposes are limited to the patient and/or the patient's designated caregiver. The MMPs will specify whether designated caregivers are permissible as well as the applicable process for registration as a designated caregiver.*<sup>14</sup>
  - *In some jurisdictions, the MMP allows an employee of a hospice provider or nursing or medical facility, or a visiting nurse, personal care attendant, or home health aide to act as a designated caregiver for the administration of medical marijuana.*<sup>15</sup>
  - *The endocannabinoid system consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids.*<sup>16</sup>
  - *Discovered in 1973, this system includes a series of cannabinoid receptors throughout the body embedded in cell membranes that, when stimulated by endocannabinoids, are thought to promote homeostasis.*<sup>17</sup>
  - *Endocannabinoids are naturally occurring substances within the body, while phytocannabinoids (plant substances that stimulate cannabinoid receptors) are found in cannabis.*<sup>18</sup>
  - *The most well known of these cannabinoids is tetrahydrocannabinol (THC); however, cannabidiol (CBD) and cannabinol (CBN) are gaining interest in therapeutic use.*<sup>19</sup>
4. The nursing student shall have an understanding of cannabis pharmacology and the research associated with the medical use of cannabis.

*Due to government restrictions on research involving cannabis, the surge of legislation has outpaced research, leaving nurses with a few resources when caring for patients who use medical cannabis. Therefore, information regarding medicinal use of cannabis must be derived from moderate to high quality evidence using randomized placebo-controlled studies. These particular studies are the most likely to elucidate causality in treatments and are the only trusted source of evidence for cannabis as a clinical intervention. Research on cannabis is an evolving body of work. As with any scientific literature, it is important to rely on the most recent high quality evidence.*

  - a. Current scientific evidence exists for the use of cannabis for the following qualifying conditions
    - *Moderate to high quality evidence exists for*
      - *cachexia*
      - *chemotherapy-induced nausea and vomiting*
      - *pain (resulting from cancer or rheumatoid arthritis)*
      - *chronic pain (resulting from fibromyalgia)*
      - *neuropathies (resulting from HIV/AIDS, multiple sclerosis {MS}, or diabetes)*
      - *spasticity (from MS or spinal cord injury).*<sup>20</sup>

b. Adverse effects of cannabis use are influenced by the patient's condition and current medications

- *The patient's propensity for the following may be exacerbated by cannabis: increased heart rate, increased appetite, sleepiness, dizziness, decreased blood pressure, dry mouth/dry eyes, decreased urination, hallucination, paranoia, anxiety, impaired attention, memory, and psychomotor performance.*<sup>21</sup>
- *Cannabis may exacerbate symptoms associated with asthma, bronchitis, and emphysema; cardiac disease; and alcohol or other drug dependence.*<sup>22</sup>
- *Cognitive impairment by cannabis may be dose- and age-dependent.*<sup>23</sup>
- *It is highly likely that cannabis will exacerbate symptoms of poor balance and posture in patients with dyskinetic disorders. Similarly, cannabis may worsen mental faculties in conditions that cause cognitive deficits. Patients who suffer from diseases with neurologic symptomology may show greater cognitive impairment.*<sup>24</sup>
- *Some participants report fatigue, suicidal ideation, nausea, asthenia, and vertigo as adverse effects of cannabis.*<sup>25</sup>
- *Cannabinoid receptors are effectively absent in the brainstem cardiorespiratory centers. This is believed to preclude the possibility of a fatal overdose from cannabinoid intake.*<sup>26</sup>
- *Cannabis can be a drug of abuse. Cannabis use disorder is defined as a problematic pattern of cannabis use leading to clinically significant impairment or distress; the clinical indications are included in the DSM-5.*<sup>27</sup>
- *Cannabis withdrawal syndrome has been identified as a syndrome seen in some patients whose cannabis use has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months). The withdrawal syndrome has varying symptomatology, including insomnia, loss of appetite, physical symptoms, and restlessness initially, then irritability/anger, vivid and unpleasant dreams after a week.*<sup>28</sup>

c. Variable effects of cannabis are dependent on type of product and route of administration

- *Since medical cannabis is not an FDA drug, there is no recommended dosage. Instead, medical cannabis dosage is titrated by the patient, with the principle of "start low, go slow."*
- *Continual patient assessment of perceived efficacy and adverse effects is recommended. Useful strategies include tracking dose, symptoms, relief, and adverse effects in a journal for review with the authorizing practitioner.*
- *FDA-approved synthetic THC drugs (dronabinol and nabilone) are administered orally or by an oromucosal route with a specific dosage.*

d. Risks to particular groups of patients

- *Adolescence. Many studies show a correlation between cannabis use and poor grades, high dropout rates, lower income, lower percentage of college degree completion, greater need for economic assistance, unemployment, and use of other drugs. Although these trends are related to recreational rather than medicinal cannabis*

*use, the trends cannot be ignored but should be balanced with the benefits of cannabis for medical use.*<sup>29</sup>

- *Fertility. Two preclinical studies indicate that interference with endogenous cannabinoids might increase chances of failed embryo implantation<sup>30</sup> and cannabinoids are capable of dysregulating hormones, which in turn can affect spermatogenesis.*<sup>31</sup>
  - *Cannabis can be a drug of abuse and precautions should be taken to minimize the risk of misuse and abuse.*
  - *Neonates. Presently there are no reliable data for neurodevelopmental outcomes with early exposure to cannabis in neonatal life, or through either breastfeeding or secondhand inhalation.*<sup>32,33,34</sup>
  - *Cannabis use may exacerbate existing psychoses in those with a risk of suicide or history of suicide attempt, schizophrenia, bipolar disorder, or other psychotic conditions.*<sup>35</sup>
5. The nursing student shall be able to identify the safety considerations for patient use of cannabis.
- *Administration of cannabis for medical use can only be carried out by the certified patient or designated caregivers registered to care for the patient.*
  - *Cannabis storage considerations include:*
    - *keeping cannabis out of the reach of children, minors, and non-registered individuals*
    - *storing all cannabis products in a locked area*
    - *keeping cannabis in the original child-resistant packaging*
    - *storing raw cannabis in a cool, dry, place*
    - *following labeling guidelines for storage and expiration dates*
  - *Disposal of unused cannabis products should be completed according to the DEA's Disposal Act.<sup>36</sup> Generally, one can locate a collection receptacle via the DEA Registration Call Center (800-882-9539).*
6. The nursing student shall approach the patient without judgment regarding the patient's choice of treatment or preferences in managing pain and other distressing symptoms.
- *Awareness of one's own beliefs and attitudes about any therapeutic intervention is vital as nurses are expected to provide patient care without personal judgment of patients.*
7. The nursing student shall be aware of medical marijuana administration considerations.
- *A nurse shall not administer cannabis to a patient unless specifically authorized by jurisdiction law.*<sup>37</sup>
  - *Instances in which the nurse may administer cannabis or synthetic THC to a patient.*
    - *Administration of FDA-approved synthetic THC drugs (dronabinol and nabilone) per facility formulary and policy*
    - *As a registered MMP designated caregiver*
      - *The majority of jurisdictions allow a designated caregiver to assist a patient with the medical use of cannabis.*
      - *These caregivers must meet specific qualifications and be registered with the MMP and must not practice outside of the limits of the caregiving statute.*<sup>38</sup>

- *Some jurisdictions allow an employee of a hospice provider or nursing or medical facility, or a visiting nurse, to assist in the administration of medical marijuana.*<sup>39</sup>
- *Check the most current MMP statute or rules.*<sup>40</sup>
- *Check facility policy regarding medical marijuana administration.*

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# Medical Marijuana Education in APRN Nursing Programs

## Purpose of the Guidelines

Over 31 US jurisdictions (including the District of Columbia), Guam, and Puerto Rico passed legislation legalizing cannabis for medical use. Several other jurisdictions also have legalized cannabis for medical use.\* Each medical marijuana program has unique characteristics. In the United States, cannabis is a Schedule I Controlled Substance. Therefore, medical cannabis is unlike most other therapeutics in that providers cannot prescribe cannabis, nor can pharmacies dispense cannabis. However, applicable jurisdiction statutes and rules provide for the manufacture, distribution, and use of cannabis for medical purposes.

These recommendations for curriculum content will provide advanced practice registered nurses (APRNs) with principles of safe and knowledgeable practice to promote patient safety when caring for patients using marijuana and when certifying a medical marijuana qualifying condition for a specific patient.

## Definitions

*Cannabis.* Any raw preparation of the leaves or flowers from the plant genus *Cannabis*. This report uses “cannabis” as a shorthand that also includes cannabinoids.

*Cannabidiol (CBD).* A major cannabinoid that indirectly antagonizes cannabinoid receptors, which may attenuate the psychoactive effects of tetrahydrocannabinol.

*Cannabinoid.* Any chemical compound that acts on cannabinoid receptors. These include endogenous and exogenous cannabinoids.

*Cannabinol (CBN).* A cannabinoid more commonly found in aged cannabis as a metabolite of other cannabinoids. It is nonpsychoactive.

*Certify* The act of confirming that a patient has a qualifying condition. Many jurisdictions use alternative phrases such as “attest”

\* In Australia, cannabis for medical use is federally legal, with states allowed to implement as they see fit. Although Bermuda has not legislated use of marijuana, their Supreme Court ruled that citizens can apply for personal licenses to possess cannabis for medical use. Cannabis for medical use is federally legal in all provinces of Canada. In New Zealand, physicians may prescribe CBD and cannabis-based products.

or “authorize”; however, 13 of 29 jurisdictions use “certify” language in their statutes.

*Clinical research.* An activity that involves studies that experimentally assign randomized human participants to one or more drug interventions to evaluate the effects on health outcomes

*Designated caregiver.* An individual who is selected by the Medical Marijuana Program qualifying patient and authorized by the Medical Marijuana Program to purchase and/or administer cannabis on the patient’s behalf. Also sometimes referred to as an “alternate caregiver.”

*Dronabinol.* The generic name for synthetic tetrahydrocannabinol. It is the active ingredient in the U.S. Food & Drug Administration (FDA)-approved drug Marinol.

*Endocannabinoid system.* A system that consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids.

*Marijuana.* A cultivated cannabis plant, whether for recreational or medicinal use. The words “marijuana” and “cannabis” are often used interchangeably in various lay and scientific literature. These guidelines will primarily use the word “cannabis.” When referring to a medical marijuana program, the guidelines will use the word “marijuana,” as it is often used within program references.

*Medical Marijuana Program (MMP.)* The official jurisdictional resource for the use of cannabis for medical purposes. Search the jurisdiction’s website or Department of Health for “medical cannabis program” or “medical marijuana program.”<sup>1</sup>

*Nabilone.* The generic name for a synthetic cannabinoid similar to tetrahydrocannabinol. It is the active ingredient in the FDA-approved drug Cesamet.

*Schedule I Controlled Substance.* Defined in the federal Controlled Substances Act<sup>2</sup> as those substances that have a high potential for abuse; no currently accepted medical use in treatment in the United States; and a lack of accepted safety for use of the substance under medical supervision.

*Tetrahydrocannabinol (THC).* One of many cannabinoids found in cannabis. THC is the primary substance responsible for most of the characteristic psychoactive effects of cannabis.<sup>3</sup>

## Recommendations

1. The APRN student shall have a working knowledge of the current state of legalization of medical and recreational cannabis use.
  - *The Drug Enforcement Agency (DEA) classifies cannabis as a Schedule I Controlled Substance. This classification not only prohibits practitioners from prescribing cannabis, it also prohibits most research using cannabis except under rigorous oversight from the government.*<sup>4</sup>
  - *The process for obtaining cannabis for federally funded research purposes is cumbersome. Currently, the only legal source of cannabis for research purposes is grown in limited quantities at the University of Mississippi.*<sup>5</sup> *The DEA sets an annual quota for cannabis grown for research purposes.*<sup>6</sup> *Applications to use this source of cannabis must be made to the FDA, DEA, and National Institute on Drug Abuse.*<sup>7</sup>
  - *Over 31 jurisdictions (including the District of Columbia), Guam, and Puerto Rico passed legislation legalizing cannabis for medical purposes. In these laws, the jurisdiction has adopted exemptions legalizing the use of cannabis for medical purposes. Although the use of marijuana pursuant to authorized MMPs conflicts with federal law and regulations, at present there is no controlling case law holding that Congress intended to preempt the field of regulation of cannabis use under its supremacy powers.*<sup>8</sup>
  - *An increasing proportion of jurisdictions have also decriminalized or legalized recreational cannabis use.*<sup>9</sup>
  - *Accordingly, the federal government's position on prosecuting the use of cannabis that is legal under applicable jurisdiction law has been set out in U.S. Department of Justice position papers. In 2009, the U.S. Attorney General took a position that discourages federal prosecutors from prosecuting people who distribute or use cannabis for medical purposes in compliance with applicable jurisdiction law; further similar guidance was given in 2011, 2013, and 2014.*<sup>10</sup> *In January 2018, the U.S. Office of the Attorney General rescinded the previous nationwide guidance specific to marijuana enforcement. The 2018 memorandum*<sup>11</sup> *provides that federal prosecutors follow the well-established principles in deciding which cases to prosecute, namely, the prosecution is to weigh all relevant considerations, including priorities set by the attorneys general, seriousness of the crime, deterrent effect of criminal prosecution, and cumulative impact of particular crimes on the community.*
2. The APRN student shall have working knowledge of the principles of an MMP.
  - *MMPs are defined and described within the statute and rules of the specific jurisdiction. The relevant statute or rules are most easily located through the jurisdiction's Department of Health and MMP.*<sup>12</sup> *Laws and rules regarding MMPs are an evolving process. Always confirm use of the most recent versions.*
  - *A health care provider does not prescribe cannabis.*
  - *The MMP will specify the qualifying conditions and the certifying process as well as the type of health care provider who can certify a qualifying condition.*<sup>13</sup>
3. The APRN student shall have an understanding of the endocannabinoid system, cannabinoid receptors, cannabinoids, and the interactions between them.
  - *Specific MMP statutes define the bona fide health care provider-patient relationship necessary for authorization to certify a patient as having a qualifying condition. Some statutes require a preexisting and ongoing relationship with the patient as a treating health care provider; others note that the relationship may not be limited to issuing a written certification for the patient or a consultation simply for that purpose.*<sup>14</sup> *Verification of the existence of the required provider-patient relationship and documentation of the certification within the jurisdiction's MMP are essential.*
  - *The MMP will specify whether an APRN can certify a qualifying condition and whether a specific course or training is required in order to participate in certifying an MMP qualifying condition.*<sup>15</sup>
  - *After the qualifying condition is certified, the patient registers with the MMP. Once registered, the patient can obtain cannabis from a jurisdiction-authorized cannabis dispensary.*
  - *Procurement and administration of cannabis for medical purposes are limited to the patient and/or the patient's designated caregiver. The MMPs will specify whether designated caregivers are permissible as well as the applicable process for registration as a designated caregiver.*<sup>16</sup>
  - *In some jurisdictions, the MMP allows an employee of a hospice provider or nursing or medical facility, or a visiting nurse, personal care attendant, or home health aide to act as a designated caregiver for the administration of medical marijuana.*<sup>17</sup>
4. The APRN student shall have an understanding of the endocannabinoid system, cannabinoid receptors, cannabinoids, and the interactions between them.
  - *The endocannabinoid system consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids.*<sup>18</sup>
  - *Discovered in 1973, this system includes a series of cannabinoid receptors throughout the body embedded in cell membranes that, when stimulated by endocannabinoids, are thought to promote homeostasis.*<sup>19</sup>
  - *Endocannabinoids are naturally occurring substances within the body, while phytocannabinoids (plant substances that stimulate cannabinoid receptors) are found in cannabis.*<sup>20</sup>
  - *The most well known of these cannabinoids is tetrahydrocannabinol (THC); however, cannabidiol (CBD) and cannabitol (CBN) are gaining interest in therapeutic use.*<sup>21</sup>
5. The APRN student shall have an understanding of cannabis pharmacology and the research associated with the medical use of cannabis.

*Due to government restrictions on research involving cannabis, the surge of legislation has outpaced research, leaving nurses with few resources when caring for patients who use medical cannabis. Therefore, information regarding medicinal use of cannabis must be derived from moderate- to high-quality evidence using randomized placebo-controlled studies. These particular studies are the most likely to elucidate causality in treatments and are the only trusted source of evidence for cannabis as a clinical intervention. Research on cannabis is an evolving body of work. As with any*

scientific literature, it is important to rely on the most recent high-quality evidence.

a. Current scientific evidence exists for the use of cannabis for the following qualifying conditions

- Moderate- to high-quality evidence exists for
  - cachexia
  - chemotherapy-induced nausea and vomiting
  - pain (resulting from cancer or rheumatoid arthritis)
  - chronic pain (resulting from fibromyalgia),
  - neuropathies (resulting from HIV/AIDS, multiple sclerosis (MS), or diabetes)
  - spasticity (from MS or spinal cord injury).<sup>22</sup>
- No human studies have confirmed evidence for neuroprotective, anti-inflammatory, antitumoral, and antibacterial effects of cannabinoids. Some preclinical animal and cellular studies do provide evidence for those effects; however, no generalizations can be made to the human population.<sup>23</sup>
- The treatment of some symptomatology might be attributed to the more general and well-known effects of cannabis. Cannabis is a known sedative, appetite stimulant, and euphoriant. Instead of cannabis treating underlying symptoms, these three cannabis effects may only mask symptoms and increase a subjective sense of well-being, which could improve self-reported quality of life in patients who have difficulty sleeping, chronic pain, or poor appetite.<sup>24</sup>

b. Adverse effects of cannabis are influenced by the patient's condition and current medications

- The patient's propensity for the following may be exacerbated by cannabis: increased heart rate, increased appetite, sleepiness, dizziness, decreased blood pressure, dry mouth/dry eyes, decreased urination, hallucination, paranoia, anxiety, impaired attention, memory, and psychomotor performance.<sup>25</sup>
- Some participants report fatigue, suicidal ideation, nausea, asthenia, and vertigo as adverse effects of cannabis.<sup>26</sup>
- Cannabis may exacerbate symptoms associated with asthma, bronchitis, and emphysema; cardiac disease; and alcohol or other drug dependence. Additionally, people with cardiac disease or alcohol or other drug dependence, or whose illnesses may be exacerbated by cannabis use should be cautioned.<sup>27</sup>
- Cognitive impairment by cannabis may be dose- and age-dependent.<sup>28</sup>
- It is highly likely that cannabis will exacerbate symptoms of poor balance and posture in patients with dyskinetic disorders. Similarly, cannabis may worsen mental faculties in conditions that cause cognitive deficits. Patients who suffer from diseases with neurologic symptomatology may show greater cognitive impairment.<sup>29</sup>
- Higher than normal blood concentrations of cannabinoids, usually from overconsumption of edible cannabis product can cause prolonged and often debilitating psychoses or hyperemesis syndrome.<sup>30</sup>

- Cannabinoid receptors are effectively absent in the brainstem cardiorespiratory centers. This is believed to preclude the possibility of a fatal overdose from cannabinoid intake.<sup>31</sup>
- Cannabis can be a drug of abuse. Cannabis use disorder is defined as a problematic pattern of cannabis use leading to clinically significant impairment or distress; the clinical indications are included in the DSM-5.<sup>32</sup>
- Cannabis withdrawal syndrome has been identified as a syndrome seen in some patients whose cannabis use has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months). The withdrawal syndrome has varying symptomatology, including insomnia, loss of appetite, physical symptoms, and restlessness initially, then irritability/anger, vivid and unpleasant dreams after a week.<sup>33</sup>

c. Variable effects of cannabis are dependent on type of product and route of administration

- The only reliably studied method for the administration of non-synthetic cannabinoids is smoked cannabis. Insufficient evidence exists for vaporized cannabis, edibles, dabbing, etc. However, FDA-approved synthetic THC drugs (dronabinol and nabilone) are administered orally or by an oromucosal route.<sup>34</sup>
- Edible cannabis products may have delayed effects.<sup>35</sup>
- Therapeutic topical applications of cannabis have not been reliably studied. Tinctures have a wide range of possible applications (oromucosal, food additive, tea, etc.) and not all methods of administration have been reliably researched. Patients must be aware that concentrations may vary from those listed and to purchase these formulations from a reliable dispensary.<sup>36</sup>
- Sublingual and mucosal sprays have the benefit of directly accessing the bloodstream. Oromucosal doses have less dosage variability than smoked cannabis and edibles, but are limited by slower absorption and lower rate of THC delivery to the brain.<sup>37</sup>
- Smoked and vaporized cannabis has the advantage of rapid absorption into the bloodstream. Vaporization creates fewer pyrolytic compounds that irritate respiratory tissue. However, both methods show significant loss of active compounds lost to combustion and exhalation.<sup>38</sup>
- Routes of administration other than oral, oromucosal, smoked, or vaporized have not been studied in a clinical setting.
- Butane honey oil (or other oils used for superheated vaporization known as "dabbing"),<sup>39</sup> hashish, and other solvent-extracted resins often carry impurities, especially when manufactured by nonprofessionals. These methods of administration have not been adequately studied in a clinical setting.

d. Principles of dosage titration

- Since medical cannabis is not an FDA drug, there is no recommended dosage.
- There is a wide variability of cannabis concentration in different cannabis preparations. Due to this wide variability, principles of dosage titration (start low, go slow) and evaluation of specific effect are beneficial.



- Patients will need to titrate their dosage to establish an efficacious and stable dosing schedule over 1 to 2 weeks.<sup>40</sup>
  - Continual patient assessment of perceived efficacy and adverse effects is recommended. Useful strategies include tracking dose, symptoms, relief, and adverse effects in a journal for review with the authorizing practitioner.
  - FDA-approved synthetic THC drugs (dronabinol and nabilone) are administered orally or by an oromucosal route with a specific dosage.
- e. Risks to particular groups of patients, such as those of child-bearing age, pregnant women, neonates, adolescents, and individuals at risk for substance abuse
- Adolescence. Many studies show a correlation between cannabis use and poor grades, high dropout rates, lower income, lower percentage of college degree completion, greater need for economic assistance, unemployment, and use of other drugs. Although these trends are related to recreational rather than medicinal cannabis use, the trends cannot be ignored but should be balanced with the benefits of cannabis for medical use.<sup>41</sup>
  - Fertility. Two preclinical studies indicate that interference with endogenous cannabinoids might increase chances of failed embryo implantation<sup>42</sup> and cannabinoids are capable of dysregulating hormones, which in turn can affect spermatogenesis.<sup>43</sup>
  - Neonates. Presently there are no reliable data for neurodevelopmental outcomes with early exposure to cannabis in neonatal life, through either breastfeeding or secondhand inhalation.<sup>44,45,46</sup>
  - Cannabis can be a drug of abuse and precautions should be taken to minimize the risk of misuse and abuse.
  - Cannabis use may exacerbate existing psychoses in those with a risk of suicide or history of suicide attempt, schizophrenia, bipolar disorder, or other psychotic conditions.<sup>47</sup>
5. The APRN student shall be able to recognize signs and symptoms of cannabis use disorder and cannabis withdrawal syndrome.
- Cannabis use disorder is defined as a problematic pattern of cannabis use leading to clinically significant impairment or distress; the clinical indications are included in the DSM-5.<sup>48</sup>
  - Cannabis withdrawal syndrome has been identified as a syndrome seen in some patients whose cannabis use has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months). The withdrawal syndrome has varying symptomatology, including insomnia, loss of appetite, physical symptoms, and restlessness initially, then irritability/anger, vivid and unpleasant dreams after a week.<sup>49</sup>
6. The APRN student shall be able to identify the safety considerations for patient use of cannabis.
- Administration of cannabis for medical use can only be carried out by the certified patient and/or designated caregivers registered to care for the patient.
  - Cannabinoids have the possibility of altering the metabolic breakdown of certain drugs. Departures from normal drug metabolism can result in higher or lower than expected plasma levels, which can cause dangerous drug interactions.<sup>50</sup> Information on possible interactions is available for the synthetic cannabinoids dronabinol and nabilone on the Drug Information Portal.<sup>51</sup> The interactions listed in the Drug Information Portal are not exhaustive and not directly transferable to nonsynthetic cannabinoids. Many of the listed interactions are probable interactions, as there are not sufficient studies into cannabinoid interactions.
- Cannabis storage considerations include:
    - keeping cannabis out of the reach of children, minors, and non-registered individuals
    - storing all cannabis products in a locked area
    - keeping cannabis in the child-resistant packaging from the store
    - storing raw cannabis in a cool, dry, place
    - following labeling guidelines for storage and expiration dates
  - Disposal of unused cannabis products should be completed according to the DEA's Disposal Act.<sup>52</sup> Generally, one can locate a collection receptacle via the DEA Registration Call Center (800-882-9539).
7. The APRN student shall be aware of medical marijuana administration considerations.
- A nurse shall not administer cannabis to a patient unless specifically authorized by jurisdictional law.<sup>53</sup>
  - Instances in which the nurse may administer cannabis or synthetic THC to a patient.
    - Administration of FDA-approved synthetic THC drugs (dronabinol and nabilone) per facility formulary and policy
    - As a registered MMP designated caregiver
      - The majority of jurisdictions allow a designated caregiver to assist a patient with the medical use of cannabis.
      - These designated caregivers must meet specific qualifications and be registered with the MMP and must not practice outside of the limits of the caregiving statute.<sup>54</sup>
      - Some jurisdictions allow an employee of a hospice provider or nursing, or medical facility, or a visiting nurse, to assist in the administration of medical marijuana.<sup>55</sup>
      - Check the most current MMP statute or rules.<sup>56</sup>
      - Check facility policy regarding medical marijuana administration.
8. The APRN student shall be aware of the ethical considerations related to the care of a patient using medical marijuana.
- In addition to ethical responsibilities under the jurisdictional law, the APRN shall approach the patient without judgment regarding the patient's choice of treatment or preferences in managing pain and other distressing symptoms. Awareness of one's own beliefs and attitudes about any therapeutic intervention is vital, as nurses are expected to provide patient care without personal judgment of patients.
  - The APRN shall take all appropriate steps to ensure that the APRN is not placed in a position where there is or may be an actual conflict, or potential conflict of interest between the APRN and a cannabis dispensary or cultivation center. A conflict of interest exists when a nurse's personal interests or concerns are or may be



*perceived as inconsistent with the best interest of the patient (e.g., when an APRN recommends a treatment in which the APRN has a financial stake).*

- *The APRN shall not certify an MMP qualifying condition for oneself or a family member. An emerging conflict of interest in the medical field is when practitioners treat their own family members. The emotional attachment to the patient may cause the practitioner's judgment to be compromised.*
9. The APRN student shall follow specific employer policies and procedures, terms of the collaborative agreement, standard care arrangement, and facility policy and procedures regarding certifying a qualifying condition.

*Always check with the facility, collaborative agreement, and local Department of Health or MMP for more information on the statutes of your jurisdiction when caring for a patient who can legally use cannabis for medical purposes.*<sup>57</sup>

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# APRNs Certifying a Medical Marijuana Qualifying Condition

## Purpose of the Guidelines

Over 31 US jurisdictions (including the District of Columbia), Guam, and Puerto Rico passed legislation legalizing cannabis for medical use. Several other jurisdictions also have legalized cannabis for medical use.\* Each medical marijuana program has unique characteristics. In the United States, cannabis is a Schedule I Controlled Substance. Therefore, medical cannabis is unlike most other therapeutics in that providers cannot prescribe cannabis, nor can pharmacies dispense cannabis. However, applicable jurisdiction statutes and rules provide for the manufacture, distribution, and use of cannabis for medical purposes.

These guidelines provide advanced practice registered nurses (APRNs) with principles of safe and knowledgeable practice to promote patient safety when certifying a medical marijuana qualifying condition.

## Definitions

*Cannabis.* Any raw preparation of the leaves or flowers from the plant genus *Cannabis*. This report uses “cannabis” as a shorthand that also includes cannabinoids.

*Cannabidiol (CBD).* A major cannabinoid that indirectly antagonizes cannabinoid receptors, which may attenuate the psychoactive effects of tetrahydrocannabinol.

*Cannabinoid.* Any chemical compound that acts on cannabinoid receptors. These include endogenous and exogenous cannabinoids.

*Cannabinol (CBN).* A cannabinoid more commonly found in aged cannabis as a metabolite of other cannabinoids. It is nonpsychoactive.

*Certify.* The act of confirming that a patient has a qualifying condition. Many jurisdictions use alternative phrases such as “attest”

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\* In Australia, cannabis for medical use is federally legal, with states allowed to implement as they see fit. Although Bermuda has not legislated use of marijuana, its Supreme Court ruled that citizens could apply for personal licenses to possess cannabis for medical use. Cannabis for medical use is federally legal in all provinces of Canada. In New Zealand, physicians may prescribe CBD and cannabis-based products.

or “authorize”; however, 13 of 29 jurisdictions use “certify” language in their statutes.

*Clinical research.* An activity that involves studies that experimentally assign randomized human participants to one or more drug interventions to evaluate the effects on health outcomes

*Designated caregiver.* An individual who is selected by the Medical Marijuana Program qualifying patient and authorized by the Medical Marijuana Program to purchase and/or administer cannabis on the patient’s behalf. Also sometimes referred to as an “alternate caregiver.”

*Dronabinol.* The generic name for synthetic tetrahydrocannabinol. It is the active ingredient in the U.S. Food & Drug Administration (FDA)-approved drug Marinol.

*Endocannabinoid system.* A system that consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids.

*Marijuana.* A cultivated cannabis plant, whether for recreational or medicinal use. The words “marijuana” and “cannabis” are often used interchangeably in various lay and scientific literature. These guidelines will primarily use the word “cannabis.” When referring to a medical marijuana program, the guidelines will use the word “marijuana,” as it is often used within program references.

*Medical Marijuana Program (MMP).* The official jurisdictional resource for the use of cannabis for medical purposes. Search the jurisdiction’s website or Department of Health for “medical cannabis program” or “medical marijuana program.”<sup>1</sup>

*Nabilone.* The generic name for a synthetic cannabinoid similar to tetrahydrocannabinol. It is the active ingredient in the FDA-approved drug Cesamet.

*Schedule I Controlled Substance.* Defined in the federal Controlled Substances Act<sup>2</sup> as those substances that have a high potential for abuse; no currently accepted medical use in treatment in the United States; and a lack of accepted safety for use of the substance under medical supervision.

*Tetrahydrocannabinol (THC).* One of many cannabinoids found in cannabis. THC is the primary substance responsible for most of the characteristic psychoactive effects of cannabis.<sup>3</sup>



## Recommendations

### Essential Knowledge

1. The APRN shall have a working knowledge of the current state of legalization of medical and recreational cannabis use.
  - *The Drug Enforcement Agency (DEA) classifies cannabis as a Schedule I Controlled Substance. This classification not only prohibits practitioners from prescribing cannabis, it also prohibits most research using cannabis, except under rigorous oversight from the government.*<sup>4</sup>
  - *The process for obtaining cannabis for federally funded research purposes is a cumbersome process and unlike any other drug research. Currently, the only legal source of cannabis for research purposes is grown in limited quantities at the University of Mississippi.*<sup>5</sup> *The DEA sets a quota for the amount of cannabis that can be grown for research studies.*<sup>6</sup> *Applications to use this source of cannabis must be made to the U.S. Food & Drug Administration (FDA), DEA, and National Institute on Drug Abuse.*<sup>7</sup>
  - *Over 31 jurisdictions (including the District of Columbia), Guam, and Puerto Rico passed legislation legalizing cannabis for medical purposes. In these laws, the jurisdiction has adopted exemptions legalizing the use of cannabis for medical purposes. Although the use of marijuana pursuant to authorized medical marijuana programs (MMPs) conflicts with federal law and regulations, at present there is no controlling case law holding that Congress intended to preempt the field of regulation of cannabis use under its supremacy powers.*<sup>8</sup>
  - *An increasing proportion of jurisdictions have also decriminalized or legalized recreational cannabis use.*<sup>9</sup>
  - *The federal government's position on prosecuting the use of cannabis that is legal under applicable jurisdiction law has been set out in U.S. Department of Justice position papers. In 2009, the U.S. Attorney General took a position that discourages federal prosecutors from prosecuting people who distribute or use cannabis for medical purposes in compliance with applicable jurisdiction law; further similar guidance was given in 2011, 2013, and 2014.*<sup>10</sup> *In January 2018, the U.S. Office of the Attorney General rescinded the previous nationwide guidance specific to marijuana enforcement. The 2018 memorandum*<sup>11</sup> *provides that federal prosecutors follow the well-established principles in deciding which cases to prosecute, namely, the prosecution is to weigh all relevant considerations, including priorities set by the attorneys general, seriousness of the crime, deterrent effect of criminal prosecution, and cumulative impact of particular crimes on the community.*
2. The APRN shall have knowledge of the jurisdiction's MMP.
  - *MMPs are defined and described within the statute and rules of the specific jurisdiction. The relevant statute or rules are most easily located through the jurisdiction's Department of Health and MMP.*<sup>12</sup> *Laws and rules regarding MMPs are an evolving process. Always confirm use of the most recent versions.*
  - *A health care provider does not prescribe cannabis.*
3. The APRN shall have an understanding of the endocannabinoid system, cannabinoid receptors, cannabinoids and the interactions between them.
  - *The endocannabinoid system consists of endocannabinoids, cannabinoid receptors, and the enzymes responsible for synthesis and degradation of endocannabinoids.*<sup>18</sup>
  - *Discovered in 1973, this system includes a series of cannabinoid receptors throughout the body embedded in cell membranes that, when stimulated by endocannabinoids, are thought to promote homeostasis.*<sup>19</sup>
  - *Endocannabinoids are naturally occurring substances within the body, while phytocannabinoids (plant substances that stimulate cannabinoid receptors) are found in cannabis.*<sup>20</sup>
  - *The most well known of these cannabinoids is tetrahydrocannabinol (THC); however, cannabidiol (CBD) and cannabitol (CBN) are gaining interest in therapeutic use.*<sup>21</sup>
4. The APRN shall have an understanding of cannabis pharmacology and the research associated with the medical use of cannabis.

*Due to government restrictions on research involving cannabis, the surge of legislation has outpaced research, leaving nurses with few resources when caring for patients who use medical cannabis. Therefore, information regarding medicinal use of cannabis must be derived from moderate- to high-quality evidence using randomized placebo-controlled studies. These particular studies are the most likely to elucidate causality in treatments*

and are the only trusted source of evidence for cannabis as a clinical intervention. Research on cannabis is an evolving body of work. As with any scientific literature, it is important to rely on the most recent high-quality evidence.

a. Current scientific evidence exists for the use of cannabis for the following qualifying conditions:

- Moderate- to high-quality evidence exists for
  - cachexia
  - chemotherapy-induced nausea and vomiting
  - pain (resulting from cancer or rheumatoid arthritis)
  - chronic pain (resulting from fibromyalgia)
  - neuropathies (resulting from HIV/AIDS, multiple sclerosis {MS}, or diabetes)
  - spasticity (from MS or spinal cord injury)<sup>22</sup>
- No human studies have confirmed evidence for neuroprotective, anti-inflammatory, antitumoral, and antibacterial effects of cannabinoids. Some preclinical animal and cellular studies do provide evidence for those effects; however, no generalizations can be made to the human population.<sup>23</sup>
- The treatment of some symptomology might be attributed to the more general and well-known effects of cannabis. Cannabis is a known sedative, appetite stimulant, and euphoriant. Instead of cannabis treating underlying symptoms, these three effects of cannabis may only mask symptoms and increase a subjective sense of well-being, which could improve self-reported quality of life in patients that have difficulty sleeping, chronic pain, or poor appetite.<sup>24</sup>

b. Adverse effects of cannabis are influenced by the patient's condition and current medications

- The patient's propensity for the following may be exacerbated by cannabis: increased heart rate, increased appetite, sleepiness, dizziness, decreased blood pressure, dry mouth/dry eyes, decreased urination, hallucination, paranoia, anxiety, impaired attention, memory, and psychomotor performance.<sup>25</sup>
- Some participants report fatigue, suicidal ideation, nausea, asthenia, and vertigo as adverse effects of cannabis.<sup>26</sup>
- People with asthma, bronchitis, and emphysema should be cautioned not to use smoked cannabis. People with cardiac disease, alcohol or other drug dependence, or whose illnesses may be exacerbated by cannabis use should be cautioned.<sup>27</sup>
- Cognitive impairment by cannabis may be dose- and age-dependent.<sup>28</sup>
- It is highly likely that cannabis will exacerbate symptoms of poor balance and posture in patients with dyskinetic disorders. Similarly, cannabis may worsen mental faculties in conditions that cause cognitive deficits. Patients who suffer from diseases with neurologic symptomology may show greater cognitive impairment.<sup>29</sup>
- Higher-than-normal blood concentrations of cannabinoids, usually from overconsumption of edible cannabis product, can cause prolonged and often debilitating psychoses or hyperemesis syndrome.<sup>30</sup>

- Cannabinoid receptors are effectively absent in the brainstem cardiorespiratory centers. This is believed to preclude the possibility of a fatal overdose from cannabinoid intake.<sup>31</sup>
- Cannabis use disorder is defined as a problematic pattern of cannabis use leading to clinically significant impairment or distress; the clinical indications are included in the DSM-5.<sup>32</sup>
- Cannabis withdrawal syndrome has been identified as a syndrome seen in some patients whose cannabis use has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months). The withdrawal syndrome has varying symptomatology, including insomnia, loss of appetite, physical symptoms, and restlessness initially, irritability/anger, then vivid and unpleasant dreams after a week.<sup>33</sup>

c. Variable effects of cannabis are dependent on type of product and route of administration

- The only reliably studied method for the administration of non-synthetic cannabinoids is smoked cannabis. Insufficient evidence exists for vaporized cannabis, edibles, dabbing, etc. However, FDA-approved synthetic THC drugs (dronabinol and nabilone) are administered orally or by an oromucosal route.<sup>34</sup>
- Edible cannabis products may have delayed effects.<sup>35</sup>
- Therapeutic topical applications of cannabis have not been reliably studied. Tinctures have a wide range of possible applications (oromucosal, food additive, tea, etc.) and not all methods of administration have been reliably researched. Patients must be aware that concentrations may vary from those listed and to purchase these formulations from a reliable dispensary.<sup>36</sup>
- Sublingual and mucosal sprays have the benefit of directly accessing the bloodstream. Oromucosal doses have less dosage variability than smoked cannabis and edibles, but are limited by slower absorption and lower rate of THC delivery to the brain.<sup>37</sup>
- Smoked and vaporized cannabis has the advantage of rapid absorption into the bloodstream. Vaporization creates fewer pyrolytic compounds that irritate respiratory tissue. However, both methods show significant loss of active compounds lost to combustion and exhalation.<sup>38</sup>
- Routes of administration other than oral, oromucosal, smoked, or vaporized have not been studied in a clinical setting.
- Butane honey oil (or other oils used for superheated vaporization known as "dabbing"),<sup>39</sup> hashish, and other solvent-extracted resins often carry impurities, especially when manufactured by nonprofessionals. These methods of administration have not been adequately studied in a clinical setting.

d. Principles of dosage titration

- Since medical cannabis is not an FDA drug, there is no recommended dosage.
- There is a wide variability of cannabis concentration in different cannabis preparations. Due to this wide variability, principles of dosage titration (start low, go slow) and evaluation of specific effect are beneficial.



- Patients will need to titrate their dosage to establish an efficacious and stable dosing schedule over 1 to 2 weeks.<sup>40</sup>
  - Continual patient assessment of perceived efficacy and adverse effects is recommended. Useful strategies include tracking dose, symptoms, relief, and adverse effects in a journal for review with the authorizing practitioner.
- e. Risks to particular groups of patients
- Adolescents. Many studies show a correlation between cannabis use and poor grades, high dropout rates, lower income, lower percentage of college degree completion, greater need for economic assistance, unemployment, and use of other drugs.<sup>41</sup> Although these trends are related to recreational rather than cannabis for medical use, the trends cannot be ignored but should be balanced with the benefits of cannabis for medical use.
  - Fertility. Two preclinical studies indicate that interference with endogenous cannabinoids might increase chances of failed embryo implantation<sup>42</sup> and cannabinoids are capable of dysregulating hormones, which in turn can affect spermatogenesis.<sup>43</sup>
  - Neonates. Presently there are no reliable data for neurodevelopmental outcomes with early exposure to cannabis in neonatal life, through either breastfeeding or secondhand inhalation.<sup>44,45,46</sup>
  - Cannabis can be a drug of abuse and precautions should be taken to minimize the risk of misuse and abuse.
  - Individuals with a risk of suicide or history of suicide attempt, schizophrenia, bipolar disorder, or other psychotic condition should be cautioned that cannabis use might exacerbate existing psychoses.<sup>47</sup>
5. The APRN shall be able to recognize signs and symptoms of cannabis use disorder and cannabis withdrawal syndrome.
- Cannabis use disorder is defined as a problematic pattern of cannabis use leading to clinically significant impairment or distress; the clinical indications are included in the DSM-5.<sup>48</sup>
  - Cannabis withdrawal syndrome has been identified as a syndrome seen in some patients whose cannabis use has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months). The withdrawal syndrome has varying symptomatology, including insomnia, loss of appetite, physical symptoms, and restlessness initially, then irritability/anger, vivid and unpleasant dreams after a week.<sup>49</sup>
6. The APRN shall have an understanding of the safety considerations for patient use of cannabis.
- Administration of cannabis for medical use can only be carried out by the certified patient and/or designated caregivers registered to care for the patient.
  - Cannabinoids have the possibility of altering the metabolic breakdown of certain drugs. Departures from normal drug metabolism can result in higher or lower than expected plasma levels, which can cause dangerous drug interactions.<sup>50</sup> Information on possible interactions is available for the synthetic cannabinoids dronabinol and nabilone on the Drug Information Portal.<sup>51</sup> The interactions listed in the Drug Information Portal are not exhaustive and not directly transferable to nonsynthetic cannabinoids. Many of the listed inter-

actions are probable interactions, as there are not sufficient studies into cannabinoid interactions.

- Storage considerations include:
  - keeping cannabis out of the reach of children, minors, and non-registered individuals
  - storing all cannabis products in a locked area
  - keeping cannabis in the original child-resistant packaging
  - storing raw cannabis in a cool, dry, place
  - following labeling guidelines for storage and expiration dates
- Disposal of unused cannabis products should be completed according to the DEA's Disposal Act.<sup>52</sup> Generally, one can locate a collection receptacle via the DEA registration Call Center (800-882-9539).

### Clinical Encounter And Identification Of A Qualifying Condition

1. The APRN shall perform a clinical assessment within the framework of a professional provider/patient relationship during an in-person encounter, including a complete assessment of the patient and a review of diagnostic information in order to identify whether the patient has a condition specified in the MMP.

*An in-person encounter is the appropriate setting for a comprehensive and systematic assessment as a foundation for decision making related to the patient's condition and whether the condition meets the qualifying conditions in the particular MMP.*

2. The APRN shall review the patient's current treatment for the qualifying condition and the response to that treatment.

*Safe practice includes review of treatment history for the qualifying condition and the effectiveness of the past and current treatment.*

3. The APRN shall complete a thorough medication reconciliation as well as a review of the jurisdiction's prescription drug monitoring program.

*Safe practice includes a thorough review of the medication history, including any potential drug precautions or interactions with cannabis.*

4. The APRN shall review the patient's mental health, alcohol, and substance use history and if present, seek a consultation or referral for that use.

*Cannabis can be a drug of abuse and precautions should be taken to minimize the risk of misuse and abuse.<sup>53</sup> Additionally, individuals with a risk of suicide or history of suicide attempt, schizophrenia, bipolar disorder, or other psychotic condition should be cautioned that cannabis use may exacerbate existing psychoses.<sup>54</sup>*

5. The APRN shall gather specific historical and current information regarding the patient's experience with cannabis and discuss the patient's values, preferences, needs, and knowledge related to cannabis use.

*Although there is a growing cultural acceptance of cannabis for medical indications, it has long been known as an illegal substance. The negotiation of patient-centered, culturally appropriate, evidence-based goals and modalities of care is necessary in nursing care, especially when discussing medical marijuana as a treatment option.*

6. The decision to certify the MMP qualifying condition is not to be predicated on the existence of a qualifying condition alone. The APRN shall consider the available scientific evidence for the specific qualifying condition prior to certifying the qualifying condition including:

- *present scientific evidence for cannabis use with the specific qualifying condition*
- *adverse effects according to the patient's clinical presentation*
- *variable effects of cannabis*
- *principles of dose titration*
- *risks to particular groups of patients, such as those of childbearing age, pregnant, neonates, adolescents, and individuals at risk for substance abuse*

7. The APRN shall determine the ongoing monitoring and evaluation of the patient.

*Active participation via ongoing monitoring, patient diaries, follow-up appointments, and evaluation of effects and response to medical marijuana is advisable.*

### **Informed and Shared Decision Making**

1. The APRN shall provide information to the patient and family members/caregivers regarding:

- *scientific evidence for cannabis for the qualifying condition*
- *adverse effects of cannabis use based on the patient's condition and current medications*
- *variable effects of cannabis*
- *lack of cannabis product standardization*
- *principles of dosage titration*
- *safety considerations for the use of cannabis*
- *individualized goals of medical marijuana therapy*
  - *Disclose to the patient that the current evidence regarding the medical use of cannabis is largely based on case reports and observational studies. The patient's response to cannabis may be different. Until more clinical evidence is collected, it is difficult to predict how cannabis will affect the patient.*
  - *Medical marijuana is not covered by health insurance and costs can vary depending on the frequency of dosage.*
- *requirements for ongoing monitoring and evaluation*
  - *Recommendations include active patient participation in ongoing monitoring via patient diary/journal, follow-up appointments, and evaluation of effects and response to cannabis.*

2. Together, the APRN and the patient shall make the decision whether or not to proceed with certifying the qualifying condition.

*When all reasonable options have been discussed, and the patient understands the possible outcomes of each option, it is the patient's right to choose the course of care.*

### **Documentation and Communication**

1. The APRN shall document the patient assessment, reasoning underlying the therapeutic use of cannabis for the qualify-

ing condition, goals of therapy, means to monitor and evaluate response, and education provided to the patient.

*Essential documentation for good clinical communication should specifically include the evidence base for any practice decisions, treatment goals, and patient education.*

2. The APRN shall communicate the patient's plan of care for use of medical marijuana to other health team members.

*Clear, complete, and accurate documentation in a health record ensures that all those involved in a patient's care have access to information upon which to plan and evaluate their interventions.*

### **Ethical Considerations**

1. In addition to ethical responsibilities under the jurisdictional law, the APRN shall approach the patient without judgment regarding the patient's choice of treatment or preferences in managing pain and other distressing symptoms.

*Awareness of one's own beliefs and attitudes about any therapeutic intervention is vital, as nurses are expected to provide patient care without personal judgment of patients.*

2. The APRN shall take all appropriate steps to ensure that the APRN is not placed in a position where there is or may be an actual conflict, or potential conflict of interest between the APRN and a cannabis dispensary or cultivation center.

*A conflict of interest exists when a nurse's personal interests or concerns are or may be perceived as inconsistent with the best interest of the patient (e.g., when an APRN recommends a treatment in which the APRN has a financial stake).*

3. The APRN shall not certify a MMP qualifying condition for oneself or a family member.

*An emerging conflict of interest in the medical field is when practitioners treat their own family members. The emotional attachment to the patient may cause a practitioner's judgment to be compromised.*

### **Special Considerations**

- Follow specific employer policies and procedures, terms of the collaborative agreement, standard care arrangement, and facility policy and procedures regarding certifying a qualifying condition.

*Always check with the facility, collaborative agreement, and local Department of Health or MMP for more information on the statutes of your jurisdiction when caring for a patient who can legally use cannabis for medical purposes.<sup>55</sup>*

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# The NCSBN Medical Marijuana Nursing Guidelines Committee

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# Quality Research, Evidence of Effectiveness of Medical Cannabis

The research studies in the table below were each evaluated using the GRADE scale (Cochrane Methods Bias, n.d.; “What is GRADE?,” 2012), a tool for assessing the quality of evidence, elucidating high, moderate, low, and very low evidence quality. All randomized experimental studies are initially rated as high quality; and observational studies began at low-quality rating. In this assessment, a study loses quality if it has serious risk of bias (from improper blinding of subjects and assessors, nonrandom sorting, patient dropout), confounding factors, imprecision, or inconsistency. Studies gain quality if the data show a large effect or dosage effect, or the study adequately controlled confounding factors.

The table below presents the moderate- to high-quality data asserting a positive effect of cannabis for qualifying conditions. The table preferentially displays therapeutic effects. Adverse effects and/or the absence of effect are not included in this table except for when they add perspective to currently debated therapeutic applications. For example, Hallak and colleagues (2010) detected no effect of CBD on schizophrenia symptomology. This is worth noting because CBD is often described as an antipsychotic (Russo & Guy, 2006), though the details and applicability of this effect continue to be researched.

The table groups the studies according to conditions with significant evidence and are preferentially grouped by qualifying condition. The conditions are listed in **bold** and subcategories are listed in *italics*. For example, Freeman et al., 2006, has data for *Incontinence* as a symptom of Multiple Sclerosis.

The studies are not generalizable. The conclusions of the studies can only be applied to the particular symptoms, conditions, and groups that were studied. The *Results* column notes the condition, symptoms, and sex of the subjects with statistically relevant results. Many of the studies can apply to more than one qualifying condition; when this occurs, those studies are grouped based on the primary qualifying condition of study (i.e., Cachexia instead of HIV).

Study	Drug (Dosage), Delivery	Grade	Results
<b>Cachexia</b>			
Abrams et al., 2003	Cannabis (3.95%THC three doses daily), smoked and dronabinol (3.93% three doses daily), oromucosal	Moderate to low	Smoked and oral cannabinoids not unsafe for HIV patients in short term. Increased weight by fat (smoked, $p = 0.021$ ; dronabinol, $p = 0.004$ ). Results applicable to male patients. $N = 62$
Andries, Frystyk, Flyvbjerg, & Støving, 2014	Dronabinol (2.5mg twice daily), orally	Moderate to high	Significant weight gain of 1.00kg during dronabinol vs 0.34kg during placebo ( $p = 0.03$ ). Results applicable to anorexic female patients. $N = 25$
Haney, Rabkin, Gunderson, & Foltin, 2005	Dronabinol (10mg, 20mg, and 30mg), orally and cannabis (1.8%, 2.8%, and 3.9% THC), smoked	Moderate to low	Cannabis and dronabinol significantly increased caloric intake in the low BIA group (10mg and 1.8%THC $p < 0.005$ , 30mg and 3.9% $p < 0.01$ ) but not in the normal BIA group. Results applicable to male patients. $N = 29$
Haney et al., 2007	Cannabis (2.0%, 3.9%THC four times daily), smoked and dronabinol (5mg, 10mg four times daily), orally	High to moderate	Cannabis (3.9%THC) improved ratings of sleep ( $p < 0.005$ ) in HIV patients. Dronabinol ( $p = 0.008$ ) and cannabis ( $p = 0.01$ ) dose dependently increased caloric intake by increasing the number of eating occasions, resulting in improved weight via fat gain. Results applicable to male patients. $N = 10$
Timpone et al., 1997	Dronabinol (2.5mg twice daily), orally	Moderate to low	Megestrol acetate showed greater weight gain than dronabinol ( $p = 0.0001$ ) and combining the two did not lead to additive weight gain in patients with HIV. $N = 39$

(continued)

Study	Drug (Dosage), Delivery	Grade	Results
<b>Cancer</b>			
Johnson et al., 2010	THC:CBD (22mg–32mg/day THC, 20mg–30mg/day CBD), oromucosal	Moderate to low	THC:CBD caused 30% reduction in pain from baseline in patients unresponsive to opioids. THC:CBD patients used a median oral morphine dose lower than other treatments. THC:CBD had a significantly improved constipation score. (OR THC:CBD = 2.81, $p = 0.006$ ) $N = 177$
<b>Chronic Pain</b>			
Narang et al., 2008	Dronabinol (10mg and 20mg THC), orally	Moderate	Total pain relief at 8 hours (TOTPAR) improved (20mg $p = 0.01$ , 10mg $p = 0.05$ ). Evoked pain (ESPID) decreased (20mg, 10mg $p < 0.05$ ). Significant reduction of pain over time (baseline vs week 2, $p = 0.01$ ; week 1 vs week 3, $p = 0.05$ ; week 2 vs week 4, $p = 0.05$ ). $N = 30$
<i>Rheumatoid Arthritis</i>			
Blake, Robson, Ho, Jubb, & McCabe, 2006	Sativex (max 6 doses daily), oromucosal	Moderate to low	Improvements in morning pain on movement ( $p = 0.044$ ), morning pain at rest ( $p = 0.018$ ), quality of sleep ( $p = 0.027$ ), (DAS28 $p = 0.002$ ), and pain at present ( $p = 0.016$ ). Results applicable to female patients. $N = 31$
<b>Epilepsy</b>			
<i>Dravet syndrome</i>			
Devinsky et al., 2017	CBD (20mg/kg/day), oromucosal	High to moderate	CBD decreased the median frequency of convulsive seizures per month (compared to placebo, $p = 0.01$ ). The Caregiver Global Impression of Change scale showed improvement in 62% of the CBD group (from baseline, $p = 0.02$ ). The frequency of total seizures of all convulsive types was reduced ( $p = 0.03$ ). $N = 120$
<i>Lennox-Gastaut syndrome</i>			
Thiele et al., 2018	CBD (20mg/kg/day), orally	High	CBD decreased the median percentage of monthly drop by 43.9% (estimated median difference between placebo $p = 0.013$ ). Monthly frequency of total seizures decreased by a median of 41.2% from baseline with CBD (difference from placebo $p = 0.0005$ ). $N = 171$
<b>Fibromyalgia</b>			
<i>Sleep</i>			
Ware, Fitzcharles, Joseph, & Shir, 2010	Nabilone (0.5mg daily), orally	High	Improved sleep over amitriptyline 10mg (Insomnia Severity Index, adjusted difference = -3.25; CI, -5.26 to -1.24), marginally better on restfulness (difference = 0.48; CI, 0.01 to 0.95). Results applicable to female patients. $N = 29$
<i>Pain</i>			
Skrabek, Galimova, Ethans, & Perry, 2008	Nabilone (2mg daily), orally	Moderate to high	Significant decreases in the VAS ( $p < 0.02$ ), Fibromyalgia Impact Questionnaire ( $p < 0.02$ ), and anxiety ( $p < 0.02$ ) at 4 weeks. $N = 40^*$
<b>HIV/AIDS</b>			
<i>Neuropathy</i>			
Abrams et al., 2007	Cannabis (3.5% THC), smoked	Moderate	>30% reduction in pain from baseline ( $p = 0.04$ ). 34% median reduction in chronic neuropathic pain (VAS $p = 0.03$ ). >30% reduction in pain was reported by 52% in the cannabis group (comparable to oral drugs used for chronic neuropathic pain). Results applicable to male patients. $N = 50$
Ellis et al., 2009	Cannabis (1%–8% THC), smoked	High	Decrease in pain intensity (Descriptor Differential Scale $p = 0.02$ ). 46% of cannabis patients achieved at least 30% pain relief. Results applicable to male patients. $N = 27$

Study	Drug (Dosage), Delivery	Grade	Results
<b>Multiple Sclerosis</b>			
Aragona et al., 2009	Sativex (average 15 doses daily), oromucosal	Moderate to low	Did not induce psychopathology and did not impair cognition. At dosages higher than those used, interpersonal sensitivity, aggressiveness, and paranoid features might arise. <i>N</i> = 17
Collin, Davies, Mutiboko, & Ratcliffe, 2007	Sativex (max 48 doses daily), oromucosal	Moderate	Spasticity improved (NRS <i>p</i> = 0.048) and 40% of patients achieved >30% benefit ( <i>p</i> = 0.014). <i>N</i> = 184
Collin et al., 2010	Sativex (max 24 doses daily), oromucosal	Moderate to low	In the per-protocol analysis, 36% achieved at least a 30% improvement in NRS spasticity scores ( <i>p</i> = 0.04). <i>N</i> = 177
Corey-Bloom et al., 2012	Cannabis (4% THC), smoked	High	Significant decrease in modified Ashworth ( <i>p</i> = 0.001), subjective pain score ( <i>p</i> = 0.008), and highness ( <i>p</i> = 0.001). <i>N</i> = 30
Vaney et al., 2004	Cannabis extract (2.5mg THC, 0.9mg CBD. Max 30mg THC daily), orally	Moderate	Lowered spasm frequency and improved mobility results not statistically significant. <i>N</i> = 57
Wade, Makela, Robson, House, & Bateman, 2004	Sativex (2.5mg–120mg daily), oromucosal	Moderate to low	Spasticity reduced (VAS <i>p</i> = 0.001). Improvement in quality of sleep ( <i>p</i> = 0.047), and Guy's Neurological Disability scale scores ( <i>p</i> = 0.048). <i>N</i> = 160
Wade, Collin, Stott, & Duncombe, 2010	Sativex (N/A), oromucosal	Moderate to low (pooled data)	~1/3 of patients gain at least a 30% improvement from baseline. A greater proportion of treated patients responded to the treatment (OR = 1.62, <i>p</i> = 0.0073), treated patients reported greater improvement (OR = 1.67, <i>p</i> = 0.030). <i>N</i> = 666
Zajicek et al., 2003	Cannabis extract (2mg–5mg THC, 1mg–25mg CBD per capsule), orally	High	Improvements in spasticity (Ashworth <i>p</i> = 0.01), pain ( <i>p</i> = 0.002), sleep ( <i>p</i> = 0.025), and spasms ( <i>p</i> = 0.038). <i>N</i> = 657
Zajicek et al., 2012	Cannabis extract (5mg–25mg THC daily), orally	High to moderate	Relief from stiffness after 12 weeks (OR 2.26, <i>p</i> = 0.004). Rating scales had significant difference in muscle stiffness, body pain, muscle spasms, sleep quality at week 4 and increasing significance on week 8 for stiffness and body pain, and an increase in significance for spasms in week 12, but a decrease in significance in sleep and body pain (became nonsignificant) in week 12 (all significance values at least <i>p</i> < 0.025). <i>N</i> = 277
<b>Multiple Sclerosis</b>			
<i>Neuropathies</i>			
Langford et al., 2013	Sativex (max 12 doses daily), oromucosal	Moderate	At the end of the treatment, a significant difference in pain score (NRS <i>p</i> = 0.028) and sleep quality (NRS <i>p</i> = 0.015). <i>N</i> = 339
Turcotte et al., 2015	Nabilone (1mg twice daily), orally	Moderate to low	Significant differences in pain intensity (VAS <i>p</i> = 0.01). Patient perceived benefit higher with nabilone and gabapentin ( <i>p</i> < 0.05). Results applicable to female patients. <i>N</i> = 15
<i>Incontinence</i>			
Freeman et al., 2006	Cannabis extract (2.5mg THC with 1.25mg CBD or 2.5mg THC. Max 25mg daily), orally	High	Both treatments improved incontinence (cannabis extract, <i>p</i> = 0.005; THC, <i>p</i> = 0.039). Pad weight reduced in both treatments ( <i>p</i> = 0.001). <i>N</i> = 630
Kavia, De Ridder, Constantinescu, Stott, & Fowler, 2010	Sativex (max 8 doses in 3 hr and 48 doses in 24 hr), oromucosal	Moderate to low	Patients failed to respond to anticholinergics before study. Significant differences in number of episodes of nocturia ( <i>p</i> = 0.010), bladder capacity (Ordinary Bladder Capacity <i>p</i> = 0.001), number of voids/day ( <i>p</i> = 0.001) total number of voids ( <i>p</i> = 0.007), impression of change (Patient's Global Impression of Change <i>p</i> = 0.005), number of daytime voids ( <i>p</i> = 0.044). Size of effect was greater for more severely affected subjects. Results applicable to female patients. <i>N</i> = 135

(continued)

Study	Drug (Dosage), Delivery	Grade	Results
<b>Chronic Pain</b>			
Rog, Nurmikko, Friede, & Young, 2005	Cannabis extract (2.5mg THC with 2.5mg CBD. Max 48 doses daily), oromucosal	High to moderate	Improvements in pain (NRS-11, $p = 0.005$ ; Neuropathic Pain Scale, $p = 0.044$ ) and sleep disturbances ( $p = 0.003$ ). Treatment effect comparable to tramadol and pregabalin in treatment of peripheral neuropathic pain. Results applicable to female patients. $N = 66$
Svendsen, Jensen, and Bach, 2004	Dronabinol (max dose 10mg daily), orally	Moderate	Median spontaneous pain intensity lowered ( $p = 0.02$ ) and pain relief score rose ( $p = 0.035$ ). Number Needed to Treat = 3.5 (poor outcome) for 50% pain relief. $N = 24$
<b>Nausea/Vomiting</b>			
Meiri et al., 2007	Dronabinol (2.5mg–20mg daily), orally	Moderate to low	Nausea absence was significantly greater in active treatment groups ( $p < 0.05$ ). Nausea intensity and vomiting/retching lowest with dronabinol. Dronabinol and ondansetron are similarly effective for chemotherapy-induced nausea and vomiting. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone. $N = 61$
Söderpalm, Schuster, & de Wit, 2001	Cannabis (8.4mg and 16.9mg THC), smoked	High to moderate	Acute feelings of nausea were reduced (8.4mg $p < 0.05$ , 16.9mg $p < 0.01$ ) and emesis was also decreased ( $p < 0.05$ ). The higher dose of marijuana significantly reduced nausea at 20 min. However, its effects are very modest relative to ondansetron ( $p < 0.05$ ). $N = 13$
<b>Neuropathies</b>			
Frank, Serpell, Hughes, Matthews, & Kapur, 2008	Nabilone (max 2mg daily), orally	Moderate to low	Dihydrocodeine is a better analgesic than nabilone (VAS $p = 0.01$ ). A small number of patients responded well to nabilone. $N = 96$ (33 of the 96 dropped out)
Karst et al., 2003	CT3 (a potent analog of THC-11-oic acid) (max 40mg and 80mg daily), orally	Moderate	Reduced pain 3 hours after intake (VAS $p = 0.02$ ). $N = 21$
Nurmikko et al., 2007	Sativex (max 48 doses daily), oromucosal	High to moderate	Significant decrease in pain (NRS $p = 0.004$ ). $N = 125$
Wallace et al., 2007	Cannabis (4%, 8% THC), smoked	High	4% THC produced delayed analgesia (Visual Analogue Scale of Pain Intensity $p = 0.027$ ), 8% THC cannabis produced an increase in pain (Visual Analogue Scale of Pain Intensity $p = 0.009$ ) after 45 minutes. $N = 19$
Ware, Wang et al., 2010	Cannabis (2.5%, 6%, and 9.4% THC, three times daily), smoked	High	Participants receiving 9.4% reported a lower average daily pain intensity (NRS $p = 0.023$ ), improved ability to fall asleep (easier, $p = 0.001$ ; faster, $p < 0.001$ ; more drowsy, $p = 0.003$ ), and improved quality of sleep (less wakefulness, $p = 0.01$ ). Anxiety and depression were improved with 9.4% (EQ-5D questionnaire $p < 0.05$ ). $N = 23$
Wilsey et al., 2008	Cannabis (7% THC or 3.5% THC), smoked	High	Decrease in pain (VAS $p = 0.02$ ). Equal anti-nociception at every time point with no difference between the doses over time ( $p = 0.95$ ). Significant differences in measures of unpleasantness ( $p < 0.01$ ) and global impression of change ( $p < 0.01$ ). $N = 38$
Wilsey et al., 2013	Cannabis (3.53% or 1.29% THC), vaporized	Moderate to high	1.29% as effective as 3.53% THC in pain relief. Increasing cumulative analgesia over time (180 min $p < 0.0001$ , 240 min $p = 0.0004$ , 300 min $p = 0.0018$ ); analgesia remained stable afterward. Decreased levels of sharpness, burning, aching pain (both doses $p < 0.001$ ). 1.29% THC more effective for burning pain ( $p < 0.0001$ ); significantly reduced aching more than the 3.53% THC and placebo ( $p < 0.0001$ ). $N = 39$



Study	Drug (Dosage), Delivery	Grade	Results
<b>Neuropathies (continued)</b>			
<i>Diabetes</i>			
Wallace, Marcotte, Umlauf, Gouaux, & Atkinson, 2015	Cannabis (1%, 4%, or 7% THC), vaporized	Moderate	There was a modest reduction in spontaneous pain (% reduction in pain: placebo, 61.2%; 1%THC, 66.7%; 4%THC, 70.3%; 7% THC, 65.5%, $p < 0.001$ for all). $N = 16$
<b>Posttraumatic Stress Disorder</b>			
Jetly, Heber, Fraser, & Boisvert, 2015	Nabilone (0.5mg–3mg at bedtime), orally	Moderate	Reduction in nightmares (CAPS Recurring and Distressing Dream scores $p = 0.03$ ), improved global impression of change (Clinical Global Impression of Change $p = 0.05$ ) and general well-being (General Well-Being Questionnaire $p = 0.04$ ). Results applicable to male patients. $N = 10$
<b>Schizophrenia</b>			
Hallak et al., 2010	CBD (300mg or 600mg), orally	Moderate	Single dose showed no effects on symptomology. $N = 28$
<b>Spinal Cord Injury</b>			
Pooyania, Ethans, Szturm, Casey, & Perry, 2010	Nabilone (max 1mg daily), orally	Moderate to low	Decrease in the spasticity (Ashworth “most involved muscle group” $p = 0.003$ ) and total Ashworth ( $p = 0.001$ ). $N = 11$
<b>Tourette Syndrome</b>			
Müller-Vahl et al., 2002	THC (5mg, 7.5mg, 10mg), orally	Moderate to low	Significant improvement of self-reported tics (Tourette’s Syndrome Symptom List $p = 0.015$ ) and obsessive compulsive behavior ( $p = 0.041$ ). Objective scores showed improvement in simple motor tics ( $p = 0.026$ ), complex motor tic ( $p = 0.015$ ), all motor tics (simple and complex motor tics) ( $p = 0.026$ ), and complex vocal tics ( $p = 0.041$ ). Results applicable to male patients. $N = 12$

#### Notes

- Brand-name and generic-name drug dosages:
  - Sativex (2.7mgTHC, 2.5mg CBD)
  - Dronabinol (2.5, 5, or 10mgTHC)
  - Nabilone (1mgTHC)
- If dosage schedule is not mentioned (i.e., daily, twice daily, at bedtime, max in 24 hr), then the study only assessed a single dose.
- An effect is considered statistically significant if the  $p$  value is greater than or equal to 0.05. Other significant effects are noted by confidence intervals, effects, and ratios (Page, 2014).
- If more than 75% of patients in a study are one sex, then results are applicable to that sex. An \* denotes that sex proportion of patients is not given.

#### Abbreviations

BIA = bioelectrical impedance analysis; CBD = cannabinoil; CI = Confidence Interval; DAS = Disease Activity Score; NRS = Numerical Rating Scale; OR = Odds Ratio; VAS = Visual Analogue Scale; THC = tetrahydrocannabinol.

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