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 cannabinol (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).

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

(continued)

Qualifying Conditions Without Cannabis Therapeutic Clinical Evidence	Shared Symptom With an Evidence-Based Qualifying Condition
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-naive 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, Hoeppner, 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.

Dyskinesis. 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, Crocamo, 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, & Nielssen, 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 (Cougle, 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 (www.pmprb-cepmb.gc.ca) report on Sativex. *Available in Canada. Not available in the United States (undergoing FDA FastTrack trials).*
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. *FDA approved. Not covered by Medicare.*
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. *FDA approved. Covered by Medicare. Insurance may cover 3%–99% of costs.*
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, www.webmd.com, and 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 (*Beek 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.