



# Benefits and adverse effects of cannabis use among adults with persistent pain

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## ARTICLE INFO

### Article history:

Received 25 September 2018

Received in revised form

4 December 2018

Accepted 10 December 2018

Available online December 13,  
2018.

### Keywords:

Cannabis use

Nursing care

Opioid use

Pain management

Persistent pain

## ABSTRACT

**Background:** Increasingly, states are legalizing cannabis for recreational use. Improved accessibility may allow adults with pain to use cannabis more liberally. Greater understanding is needed about how adults with pain perceive the effects of cannabis, particularly those who also use opioid analgesics.

**Purpose:** To examine the perceived effects of cannabis among adults who have been prescribed opioids for persistent pain.

**Methods:** A survey-based study was conducted on 150 adults with persistent pain. Data from two open-ended questions were analyzed using a qualitative descriptive approach and content analysis.

**Findings:** Data analysis led to identification of two main categories and five subcategories: (a) cannabis benefits with two subcategories of “physiological” and “mental health”; (b) adverse effects with three subcategories of “physiological,” “mental health,” and “social and economic concerns.”

**Discussion:** Both positive and negative effects of cannabis were described. Nursing practice, including open communication with patients, can be guided by patient perspectives surrounding benefits and adverse effects of cannabis use.

**Cite this article:** Bigand, T., Anderson, C.L., Roberts, M.L., Shaw, M.R., & Wilson, M. (2019, May/June). Benefits and adverse effects of cannabis use among adults with persistent pain. *Nurs Outlook*, 67(3), 223–231. <https://doi.org/10.1016/j.outlook.2018.12.014>.

## Background

In the United States today, the prevalence of pain conditions is high, with an estimated 25 million adults experiencing pain lasting 3 months or more (Nahin, 2015). Among adults with persistent pain, co-occurring, complex symptoms such as anxiety (de Heer et al., 2014), depression (Hooten, 2016; Rayner et al., 2016), and poor-quality sleep (Finan, Goodin, & Smith, 2013) can exacerbate the pain experience and negatively impact quality of life (Kroenke et al., 2013). Many adults

with persistent pain who use opioid medications for pain management also report using cannabis to treat pain and related symptoms (Sexton, Cuttler, Finnell, & Mischley, 2016; Wilson et al., 2018). While clinical trials have found modest evidence for the effectiveness of cannabis as a pharmacotherapy for pain (Whiting et al., 2015), the experience of pain and the efficacy of marijuana for treating pain can be subjective, involving sensory, emotional, social, and genetic parameters (Hill, Palastro, Johnson, & Ditre, 2017).

Pain management is an issue of public interest in the United States, given that poorly treated pain is

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<https://doi.org/10.1016/j.outlook.2018.12.014>

referenced as the most common reason for opioid misuse (Weiss et al., 2014). “Misuse,” or taking a drug in a manner or dose other than how it was prescribed, can result in serious medical consequences (National Institute on Drug Abuse, 2018). Consequently, an opioid epidemic has been declared in the United States, resulting from increases in opioid overdose and death (Kolodny et al., 2015). In 2016 alone, over 11 million Americans reported misuse of opioid pain relievers (Substance Abuse and Mental Health Services Administration, 2017), while >40,000 people died of a drug overdose involving opioids (Centers for Disease Control, 2017). A recent study found rates of self-reported opioid misuse in adults with persistent pain to be 35%, similar to estimates of opioid misuse in the general population (Chang, 2018). However, some research suggests that the increased accessibility to cannabis will reduce opioid use (Bradford & Bradford, 2016) as cannabis may offer an alternative to opioids for pain treatment (Corroon, Mischley, & Sexton, 2017; Vyas, LeBaron, & Gilson, 2018).

The accessibility of cannabis has greatly expanded in recent years, due in large part to an increasing number of states legalizing cannabis for medical and recreational use (National Conference of State Legislatures, 2018). In contrast, the U.S. Drug Enforcement Administration classifies cannabis as a schedule 1 controlled drug, on par with heroin and cocaine (U.S. Department of Justice, 2017). As a result, some pain specialists have reported that they will not accept nor treat patients in their practice who use cannabis, even in states where cannabis is legal (Lucas and Walsh, 2017; Walsh et al., 2013). However, the increase in accessibility to cannabis may allow patients to use the drug more freely and to self-treat pain or other symptoms without the guidance of a licensed health care professional. Such medically unmonitored use may have negative side effects and can facilitate a cannabis use disorder (American Psychiatric Association, 2013; Lev-Ran et al., 2014; NAS, 2017). Nurses may play an important role in identifying cannabis use in this population by utilizing open communication, a nonjudgmental approach, and offering current research findings on the impact of cannabis use on pain and related complex symptoms as outlined by National Council on State Board of Nursing in a 2018 publication of nursing care guidelines.

In the context of the limited legal status of cannabis in selected U.S. states, there is little knowledge about how people with persistent pain perceive the benefits or adverse effects of cannabis use. Research on actual benefits and harms is also lacking due to constraints on conducting cannabis research (National Academies of Sciences, 2017; Nugent et al., 2017). The purpose of this study was to describe the perceived effects of cannabis use among people with persistent pain who are prescribed opioids in a state where it has been legalized for medical and recreational reasons. We are guided by Individual and Family Self-Management Theory (IFSMT) that incorporates holistic patient-provider communication into care of the client with

a chronic condition to empower the individual to self-manage symptoms with the help of an appropriate social network (Ryan & Sawin, 2009). Therefore, we focus on patient perceptions in this study to best understand how patients self-manage symptoms related to persistent pain using cannabis. Findings from this study may facilitate open nurse-patient communication on the perceived advantages and disadvantages of cannabis use among adults with persistent pain regarding cannabis as a pain management option.

## Methods

A qualitative descriptive approach as described by Sandelowski (2000) was used to guide the study design. Qualitative descriptive methodology is an appropriate approach when the purpose of the study is to describe participants' common beliefs, attitudes, feelings, and details about an unexplored phenomenon (Sandelowski, 2000). This study was part of a larger project that aims to examine self-reported health outcomes for adults using cannabis and opioids (Wilson et al., 2018). Two open-ended questions that have not yet been explored were the focus of this present study regarding participants' perspectives about cannabis use effects. The questions were analyzed with qualitative content analysis methods (Graneheim & Lundman, 2004) to identify common themes. In addition, a cannabis use questionnaire and demographics section were analyzed with frequency statistics to characterize the sample using IBM SPSS version 25 (IBM Corp, 2017).

## Ethical Considerations

The institutional review board from the primary investigator's university deemed this study exempt from federal regulations for human research. Permission was granted from the providers of participating pain management clinics to conduct the study. Verbal informed consent was obtained from all participants prior to entering the study. Participants were reminded of their option to stop participating at any time and the confidential nature of personal data.

## Participants and Settings

One hundred and fifty adult-receiving opioids for persistent pain conditions from three separate pain management clinics in Washington state participated in the study. A convenience sampling technique was used, and participants were recruited in the waiting rooms of the pain clinics during business hours. Research assistants provided written and verbal descriptions of the study purpose, potential benefits or adverse effects of participation, and the primary investigator's contact information. Participants were

considered eligible if they were over the age of 18 years, taking a prescription opioid medication for a practitioner-diagnosed persistent pain condition including pain related to cancer, able to provide verbal consent, and could read, write, and understand the English language.

### Data Collection and Analysis

Two open-ended survey items were used to gather participants' unique perspectives about cannabis use. The items were (a) "Please share any benefits you have experienced from using marijuana" and (b) "Please share any negative effects you have experienced from using marijuana." Participants completed surveys in clinic waiting rooms in a pen-and-paper format after verbal consent was provided. Once each survey was checked for completion by a research assistant, participants received a \$20 gift card as compensation for their time. Participants were asked to complete a demographics section to characterize the sample. Participants also completed questions about cannabis use within the survey. Specifically, participants were asked to indicate if cannabis had ever been used (yes/no), if it had been used in the past month (yes/no), how many days it had been used in the past month (0, 1–2, 3–5, 6–9, 10–19, 20–29, all 30 days), and reason(s) for use (recreation/social, pain, sleep, anxiety/stress, withdrawal, other). Responses to the cannabis questionnaires were analyzed with descriptive statistics using SPSS (version 25) to characterize cannabis use among the sample.

The qualitative data from the semistructured items were analyzed using qualitative content analysis methods (Graneheim & Lundman, 2004). While using Graneheim and Lundman's (2004) methods, participant quotes are referred to as units of analysis. Common words or statements that relate to each other through content and context are referred to as meaning units. Meaning units were identified prospectively within content areas of both perceived benefits and adverse effects of cannabis use (Graneheim & Lundman, 2004). Meaning units were further condensed and abstracted, allowing a comparison based on similarities and differences of the meaning units into subcategories (Graneheim & Lundman, 2004). During analysis, constant comparison, reflection, and interpretation occurred and the resulting categories were reviewed by the research team to evaluate for consensus.

### Findings

#### Description of Sample

Participants in the study all reported persistent pain and were between the ages of 19 through 85 years, with a median age of 52 years. The majority (68.7%) of the sample was female. Only 16.0% of the sample reported working at least part time, and consequently, 73.9% of the sample reported an annual income of <\$40,000. Nearly 80% of the sample self-reported a Caucasian

ethnicity, consistent with the demographics of the geographic location surveyed. The Morphine Equivalence Dose of self-reported daily prescription opioids taken by the sample varied greatly, from 4.5 mg to 630 mg with an average of  $64.6 \pm 76.2$  mg. The range of years reported by participants taking currently prescribed opioids was between <1 year up to 21 years with a mean of  $6.7 \pm 6.3$  years. See Table 1 for more demographics.

#### Cannabis Use Patterns of Sample

When asked if cannabis had ever been used, 69.3% ( $n=104$ ) of participants indicated yes. When questioned about use in the past 12 months, 49.3% ( $n=74$ ) of participants responded positively. In our sample, a total of 27.3% ( $n=41$ ) reported using cannabis in the last month, with 12.0% ( $n=18$ ) of the participants reporting that they used cannabis for 20 or more days in the past month. Notably, only 10.7% ( $n=16$ ) of the sample disclosed a current registration as a medical marijuana patient. A total of 75.3% of participants responded to the question addressing the benefits of cannabis use, with 70.6% responding to the question asking about the adverse effects of cannabis. When removing responses such as "none," or "n/a," 33.0% ( $n=50$ ) of the sample provided a response to the benefit question, 30.0% ( $n=45$ ) reported an adverse effect, and 16.0% ( $n=24$ ) of the sample reported both a benefit and adverse effect of cannabis use.

For those with chronic pain who reported a rationale for cannabis use ( $n=67$ ), 59.7% indicated more than one motive for use and 13.4% reported four or more reasons for use. Pain was the most frequently cited reason for use (67.2%) followed by sleep (58.2%), and recreation/social (49.3%). See Table 2 for further information on the frequency of specific reasons provided by participants regarding their use of cannabis.

#### Content Analysis Findings

Content analysis methods identified two major categories describing participants' perspectives about cannabis use with five supporting subcategories (Table 3). Nearly all of the participants' comments described either benefits or adverse effects of cannabis use with very few general comments offered, which would fall into a "neutral" category; therefore, two main categories of perceived benefits and adverse effects were identified in the data. Subcategories of similar meaning units emerged that further describe the two main categories.

#### Perceived Benefits

##### Physiological Symptom Management

Physiological symptom management emerged as one of the key perceived benefits to cannabis use among our participants. The majority who reported symptom relief stated that cannabis was helpful for pain and insomnia.

**Table 1 – Participants' Characteristics (N = 150)**

Gender	n	%	Missing*
Female	103	68.7	0
Male	47	31.3	
Household income			
<\$20,000	78	56.5	12
\$20–39,000	24	17.4	
\$40–99,000	31	22.5	
\$100,000+	5	3.6	
Highest level of education			
<High school	12	8.0	0
High school/GED diploma	35	23.3	
Some college	42	28.0	
Associate or technical certificate	37	24.7	
Bachelor's degree	16	10.7	
Graduate degree	8	5.3	
Marital status			
Married or widowed	51	35.4	6
Divorced or separated	58	40.2	
Living with partner	8	5.6	
Never married/other	27	18.8	
Employment status			
Full time	18	12.0	0
Part time	6	4.0	
Unemployed	3	2.0	
Disabled	83	55.3	
Retired	27	18.0	
Student	3	2.0	
Homemaker	3	2.0	
Other	7	4.7	
Race			
White	119	79.9	1
American Indian/Alaska Native	12	8.0	
Black	6	4.0	
Asian America	1	0.7	
Multiracial	9	6.0	
Other	2	1.3	
Registered medical marijuana patient			
Yes	16	10.7	1
No	133	89.3	

\*Question was skipped by the participant.

I do take opioids and they do help, however, smoking or eating marijuana [sic] products helps with

calming the nerves so I won't have as many muscle spasms.

**Table 2 – Reasons for Cannabis Use**

	n	%	Missing*
Recreation			
Yes	33	49.3	83
No	34	50.7	
Pain			
Yes	45	67.2	83
No	22	32.8	
Sleep			
Yes	39	58.2	83
No	28	41.8	
Anxiety/stress			
Yes	27	40.3	83
No	40	59.7	
Withdrawal			
Yes	2	3.0	83
No	65	93.0	

\*Question was skipped by the participant.

I use for medical only. (Cannabis) helps me sleep and relax most important takes away or helps pain.

Participants reported using cannabis to help with physical issues, such as falling and staying asleep, increasing appetite, and reducing pain, nausea, or other symptoms related to cancer, scleroderma, headache, neuropathies, muscle spasms, and Crohn's

**Table 3 – Categories and Subcategories**

Categories	Subcategories
Perceived benefits	1. Physiological symptom management 2. Mental health symptom management
Adverse effects	1. Physiological concerns 2. Mental health concerns 3. Social and economic concerns



disease. The easy access from legalization was mentioned by some participants as influencing their purchases for symptom relief.

With the availability of CBD and very good labeling I can pick what I need and get constant results for pain relief and sleep aid.

#### *Mental Health Symptom Management*

Participants reported that cannabis improved emotional and mental well-being, such as by reducing anxiety, depression, and stress. Several reported using cannabis to successfully cope with “PTSD” (post-traumatic stress disorder) or “depression relief.” Cannabis was also perceived to help with “anxiety” and “stress relief.” A sense of psychological well-being was conveyed in comments, including the following:

It’s (cannabis) beneficial for multiple purposes ... helps me recognize bad habits. Afterward, I am more progressive without having to have more.

I have real anxiety issues and it (cannabis) really calms me.

Other participants stated they used cannabis as a tool “for fun,” to “improve overall happiness,” for “relaxing help,” or even “to tolerate life.”

#### **Adverse Effects**

##### *Physiological Concerns*

Physiological concerns were defined as negative physical influences on the body that were perceived by some respondents to occur as a result of cannabis use. Reported effects ranged from minor consequences, such as eating too much, coughing, and weight gain, to more severe outcomes, such as seizures and anaphylaxis from an allergic reaction. Participants reported the possibility of cannabis causing “lung problems” and “fatigue that ruins the next day.” Other negative physiological symptoms included burning red eyes, dry mouth, nausea, and racing heart. A few participants conveyed periods of trial and error that would sometimes result in them stopping cannabis use.

For some reason it inflames my sciatic nerve, so I don’t use it anymore.

... sometimes I would have bad dreams so I would not partake.

##### *Mental Health Concerns*

Mental health concerns encompassed negative emotional experiences and psychological symptoms perceived by participants from cannabis use. Lack of concentration and “fuzzy thinking” was commonly reported, along with poor memory and sleepiness. A

feeling of apathy or lack of motivation was sometimes conveyed.

The high; I felt dumb, disoriented and spacey.

When I used it regularly, it made me stupid [sic].

More severe psychological disturbances were also reported and included increased anxiety, rumination, or paranoia. One reported feeling “like on a trip of acid or hallucinations.” The unpredictable nature of the effects was reported by one as a negative outcome, while another simply stated “I don’t like the feeling.”

##### *Social and Economic Concerns*

The subcategory of social and economic concerns illuminates participants’ perspectives about the negative impact of cannabis use on social and financial aspects of their lives. Some reported that the cost was “too high,” while another reported, “When I did use, I was always broke.”

I am low income and it’s (cannabis) kind of expensive so I don’t do it often. Only on really bad days.

The judgment of others about cannabis use was also conveyed as a negative social consequence. One participant stated that “I’m very private about it (cannabis use).” Another responded that a reason to avoid cannabis use was “people’s judgment.” Although most participants did not describe health care providers creating barriers to using cannabis, a few participants did share experiences of perceiving providers as having negative beliefs about use. For example, one participant stated, “doctors won’t allow it.”

## **Discussion**

This study focused on the effects of using cannabis as seen through the perspective of adults with persistent pain who are prescribed opioids. Positive benefits and adverse effects emerged from the analysis as two main categories at approximately equivalent rates among respondents (33% and 30%, respectively). About 16% of study participants indicated that cannabis had both benefits and adverse effects for them. Under benefits of cannabis use were subcategories of physiological and mental health symptom management. For adverse effects, three subcategories were identified: physiological, mental health, and social/economic concerns. Study findings are important for nurses and other health care providers who discuss complex symptom management among adults with persistent pain. Cannabis is being used in the hopes of alleviating symptoms, so nurses have a duty to engage in informed conversations with their patients about expected outcomes from its use ([National Council on State Board of Nursing, 2018](#)).

In our study, nearly half of respondents cited using cannabis for recreational or social purposes in addition to improving symptom control, a finding that corresponds to previous studies on cannabis use in chronic pain populations (Degenhardt et al., 2015; Schauer, King, Bunnell, Promoff, & McAfee, 2016). About 33% of those surveyed reported cannabis use within the past month, with 12% reporting at least weekly use. Studies surveying cannabis use among adults with persistent pain in states with legalized recreational cannabis report similar frequencies to those observed in our study. For example, 36.0% used cannabis as reported by Lucas and Walsh (2017) and 18.0% was noted in a study by Nugent et al. (2018). In contrast, only 8.3% cannabis use was reported in a state without legal cannabis for recreational purposes (Degenhardt et al., 2015). Legal and policy decisions thus may be influencing cannabis use habits among people with pain.

Pain has been previously reported as a common symptom targeted by people who use cannabis (Sexton et al., 2016; Wilson et al., 2018). The qualitative responses in our study provide evidence that pain was a major symptom perceived to be improved through cannabis use among patients with persistent pain. More than 67% endorsed using cannabis to alleviate pain, suggesting that prescribed medications may not provide sufficient pain relief in the patient's view. Along with pain, nausea is a common condition treated with medical cannabis (Hill, 2015). Cannabis can be an effective appetite stimulant by increasing the desire to eat within the brain (Koch et al., 2015). Some participants in our study indicated that cannabis helped manage gastrointestinal symptoms and stimulate appetite. Similarly, in a qualitative study by Osborn et al. (2015), participants endorsed cannabis use for gastrointestinal symptoms. Of note, although cannabis has been prescribed as a treatment for chemotherapy induced nausea since 1985 (Throckmorton, 2016), only a small percentage in our sample reported having cancer-related pain ( $N = 5.3\%$ ) and this did not emerge as an important theme in our data.

There is an interplay between pain and distressing emotional symptoms that may be difficult to disentangle for people using opioids and cannabis together (Wilson et al., 2018). Our study participants reported negative mental health symptoms like anxiety and paranoia from cannabis use. Recent reviews have found strong evidence linking cannabis use with the development of symptoms of psychosis over the short and long term (National Academies of Sciences, 2017; Nugent et al., 2017). Additionally, moderate evidence links cannabis use to increased mania in individuals diagnosed with bipolar disorders (Gibbs et al., 2015). Direct concern to health professionals is the increasing potency of cannabis products (ElSohly et al., 2016), which can induce paranoia and may lead to more permanent psychotic disorders (Farah, 2017; Volkow, Baler, Compton, & Weiss, 2014). Furthermore, heavier cannabis use is linked to increased suicidal behaviors (Delforterie et al., 2015; NAS, 2017). The discrepancy between patient beliefs and

the available science regarding mental health outcomes is of high importance to reduce risks of negative psychological effects. Nurses play an important role in educating patients on the most current evidence regarding cannabis use for mental health symptoms.

Feeling disoriented or that thinking is slowed were negative effects noted by our participants. Research suggests that the cumulative effects of cannabis on cognitive functioning can be long-lasting, leading to decreases in verbal memory, processing speed, and executive functioning (Auer et al., 2016). This potential, coupled with effects of opioids on mentation and respiratory status, could increase risks of overdose deaths when cannabis and opioids are paired, although data on the combined adverse effects of opioids and cannabis are limited (Nugent et al., 2017). Adverse effects like somnolence and impaired sleep cycle are commonly reported by people who use cannabis (Whiting et al., 2015). While 58.2% of the participants in this study used cannabis to improve their sleep, there is little corroborating evidence in literature that cannabis can actually improve sleep (Nugent et al., 2017), with some evidence suggesting that sleep quality may improve when cannabis use is reduced (Hser et al., 2017). Cannabis use for medical purposes should thus be individualized and alternatives presented for managing sleep.

A few serious adverse effects were reported from our participants including a life-threatening anaphylaxis event. While rare, there is evidence that cannabis can cause allergic response. A recent multinational review found many studies supporting evidence for allergic reactions in response to cannabis use (Chatkin, Zani-Silva, Ferreira, & Zamel, 2017). Another participant reported seizure activity after use, and still another felt that cannabis use increased pain. Case reports have been published on cannabis-induced seizures (Keshava, Rao, & Khan, 2015), despite other evidence that cannabis may reduce seizure activity (Suraev et al., 2017). While many adverse effects have been associated with cannabis use, there have been no reported incidences of overdoses involving solely cannabis, making it a potentially safer alternative than opioid use for pain management (Vyas et al., 2018). Still, nurses and health care providers need to communicate to patients that despite common perceptions, cannabis is not always a safe drug, free from side effects or the possibility of addictiveness (Berg et al., 2015).

Financial costs of cannabis may serve as significant barriers to the use of cannabis for therapeutic purposes (Lucas et al., 2015). More than 58% of our sample reported an income below the federal poverty line for a family of three (HealthCare.gov, 2018). Similarly, in a study by Lucas and Walsh (2017), 60.0% of respondents reported difficulty paying for medical cannabis, and 53% indicated having had to choose between purchasing cannabis and paying for living expenses during the past year.

Other negative aspects of cannabis use perceived by participants in this study related to barriers to medical

access. Pain specialists have been found to decline to accept or continue treatment of patients who use cannabis despite a state's stance on legality of cannabis (Lucas and Walsh, 2017; Walsh et al., 2013). Fewer than 11% of the participants in this study reported having a registered medical marijuana card, yet 33% reported marijuana use in the past month. Thus, adults with persistent pain may seek to purchase cannabis products from retail stores when able rather than engage in the medical marijuana registration process. Concerns regarding stigma associated with the use of cannabis have been cited in the literature (Bottorff et al., 2013). Our participants endorsed the feeling of being judged by others due to cannabis use. Nurses are in the ideal position to advocate for nonjudgmental care and promote open dialogues regarding cannabis use that can mitigate harm for those living with pain (Wilson, Shaw, & Roberts, 2018).

Emerging evidence suggests that certain drug–gene and drug–drug–gene interactions can make medications less potent and diminish desired symptom management outcomes for adults with persistent pain (Knisely et al., 2017), though research is lacking on how cannabis interacts with medications such as opioids. Thus, it is imperative for patients and nurses or other health care providers to discuss cannabis use and potential harms and benefits including potential interactions with other medications within the context of a medical appointment. Guidelines on care of the patient using cannabis published by the NCSBC (2018) are an important resource for nurses, particularly those working in states where medical and/or recreational cannabis is legal as cannabis use may be more frequent in these areas.

### Limitations and Strengths

The present study had several limitations and strengths to note. First, the study relied on self-report for all collected data. While self-report may be as reliable as using medical records for data verification, it is possible that participants' answers reflect an incomplete picture of reality. Furthermore, this study used two open-ended questions embedded within a larger survey study that required at least 30 min to complete. The result was limited participant responses to the item of analysis for this study, generally including one- or two-word answers, potentially due to participant response fatigue. Future studies using in-depth qualitative interviews focused on the experience of cannabis use for the adult with persistent pain using prescription opioids may provide richer data and themes. The single geographic area is a limitation, although paired with other studies, our findings suggest some commonalities may exist despite location or political landscapes. As a strength, the current study addresses a little-known phenomenon and raises important clinical implications for nurses and other health care providers regarding participant perspectives of cannabis use in the context of persistent pain conditions.

### Conclusion

Adults with persistent pain conditions suffer a variety of complex health symptoms and may seek various therapies to alleviate burdensome symptoms, including cannabis use. In this study, adults with persistent pain reported several benefits and adverse effects of cannabis. The increase in legalization of cannabis for medical and recreational use across the United States makes this new knowledge from the patient perspective especially timely. Nurses should educate themselves on current policy specific to their state of employment and be familiar with research regarding effects of cannabis on pain-related symptoms. Understanding how adults with persistent pain are using and responding to cannabis can aid open communication between patients, nurses, and other health care providers regarding safe treatment options. Nurses are in a unique position to develop trusting relationships that can encourage disclosure from patients regarding cannabis use and result in informed, shared decision-making. Respect for patient preferences should be combined with clinical knowledge and research evidence to support choices about cannabis use among adults with persistent pain using prescription opioids.

### Acknowledgments

This work was supported, in part, by Washington State University Grand Challenges Seed Grant (Grant No. WSU128515). The authors wish to acknowledge Rebecca M. Craft, PhD, Department of Psychology, Washington State University, for her contributions as Primary Investigator on the WSU Grand Challenges Seed Grant that supported this subproject.

### Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.outlook.2018.12.014](https://doi.org/10.1016/j.outlook.2018.12.014).

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