CLINICAL GUIDELINE

Cannabis or Cannabinoids for the Management of Chronic Noncancer Pain: Best Practice Advice From the American College of Physicians

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Description: The American College of Physicians' Population Health and Medical Science Committee (PHMSC) developed this best practice advice to inform clinicians about what is currently known about the benefits and harms of cannabis or cannabinoids in the management of chronic noncancer pain and to provide advice for clinicians counseling patients seeking this therapy.

Methods: The PHMSC considers areas where evidence is uncertain or emerging or practice does not follow the evidence to provide clinical advice based on a review and assessment of scientific work, including systematic reviews and individual studies. Sources of evidence included a living systematic review on cannabis and cannabinoid treatments for chronic noncancer pain and a series of living systematic reviews and primary studies.

Best Practice Advice 1a: Clinicians should counsel patients about the benefits and harms of cannabis or cannabinoids when patients are considering whether to start or continue to use cannabis or cannabinoids to manage their chronic noncancer pain.

Best Practice Advice 1b: Clinicians should counsel the following subgroups of patients that the harms of cannabis or cannabinoid use for chronic noncancer pain are likely to outweigh the benefits: young adult and adolescent patients, patients with current or past substance use disorder, patients with serious mental illness, and frail patients and those at risk for falling.

Best Practice Advice 2: Clinicians should advise against starting or continuing to use cannabis or cannabinoids to manage chronic noncancer pain in patients who are pregnant or breastfeeding or actively trying to conceive.

Best Practice Advice 3: Clinicians should advise patients against the use of *inhaled* cannabis to manage chronic noncancer pain.

Ann Intern Med. 2025;178:714-724. doi:10.7326/ANNALS-24-03319
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 4 April 2025.
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Cannabis is a genus of the flowering plant Cannabaceae. Cannabis is the term many use for products derived from the plant and is the term we will use throughout this article. Cannabinoids are compounds that exert effects through their interaction with the endocannabinoid system and can be plant derived or synthetic. When evidence clearly distinguishes, we use the term cannabinoids to refer to synthetic cannabinoids. Cannabis is currently a federally illegal substance in the United States. However, as of 2024, cannabis was legal for adult recreational and medical use in 24 U.S. states and the District of Columbia and legal only for medical use in an additional 14 states (1). Clinicians can prescribe only the 3 cannabinoids approved by the U.S. Food and Drug Administration: dronabinol (a synthetic form of delta-9-tetrahydrocannabinol [THC] approved for chemotherapy-induced nausea or HIV-associated cachexia), nabilone (a cannabinoid receptor 1 or CB1 agonist approved for chemotherapy-induced nausea), and a highly purified formulation of cannabidiol (CBD) (approved for the treatment of Dravet syndrome, Lennox–Gastaut syndrome, and seizures associated with tuberous sclerosis) (2). Currently, no cannabinoids are approved for the treatment of chronic pain. However, patients can legally access cannabis for chronic pain in most parts of the United States, either directly from a recreational store or from a medical dispensary with a certification signed by a clinician authorizing use for a qualifying medical condition. The list of qualifying conditions varies across states, but all include chronic pain (3). In

See also:

Web-Only
Supplement

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these cases, the clinician typically does not specify a product or dose of cannabis, but rather patients present their certification to a dispensary worker who then recommends products.

Cannabis for recreational and medical purposes has grown more accepted, accessible, and used in recent years (4). A national survey estimates that 81% of U.S. adults believe cannabis has at least 1 health-related benefit (5). There has been an increase in reported cannabis use across adults in many age, race and ethnicity, income, and education groups (6, 7). In 2022, 23% of U.S. adults reported using cannabis at least once in the past year (8), and the prevalence of daily or near-daily use of cannabis was 40% among persons aged 12 years and older who reported using cannabis in the past month (9). Among persons who use cannabis for medical purposes, chronic pain is the most common reason or self-identified symptom (10, 11), but the distinction between medical and recreational use can be unclear (12, 13). Over recent decades, the potency of available cannabis products—measured as the concentration of THC—has increased (14, 15). However, public perception that there are potential risks associated with cannabis use has decreased (5, 16, 17).

Patients report a desire to discuss cannabis use with their clinicians but report receiving most of their information about cannabis from dispensary workers (18, 19). Dispensary workers typically do not have medical training and do not conduct the type of individualized discussions about benefits and harms that occur in health care settings (20). Clinicians report being inadequately prepared to discuss cannabis with patients (21–23). Given the increasing prevalence of cannabis use for chronic noncancer pain, this best practice advice aims to inform clinicians of the evidence regarding the benefits and harms of cannabis in the management of chronic noncancer pain, highlight populations at high risk for adverse events, and provide advice for counseling patients about cannabis for chronic noncancer pain.

Cannabis Basics

The complexity of the plant, *Cannabis sativa,* is one of the challenges in evaluating the medical use of cannabis. When referring to any product derived from the plant, many use the term cannabis, but the term has become interchangeable with colloquial terms such as marijuana, weed, and pot. Cannabis includes multiple types of compounds, including cannabinoids, flavonoids, and terpenes. Cannabinoids are the most clinically relevant of these compounds and exert effects through their interaction with the endocannabinoid system receptors CB1, concentrated in the central nervous system, and CB2, found in peripheral tissues, including immune cells. They can be whole plant–derived or synthetic (24, 25). There are dozens of cannabinoids, for which most clinical effects remain unstudied. The 2 best-studied cannabinoids are THC and CBD. Delta-9-tetrahydrocannabinol has a high affinity for CB1 receptors, which accounts for much of the intoxicating effect of cannabis. Cannabidiol, which has lower CB1 binding affinity, is not associated with intoxication, although it may have anxiolytic and antipsychotic properties (26).

Consumption can vary along several axes: potency of the product (which usually refers to the THC concentration), additional cannabinoid content, amount and frequency used, routes of administration, and formulation. All of these influence the pharmacologic effects of cannabis and cannabinoids (27, 28).

See the **Supplement** (available at Annals.org) for a summary of basic information about cannabis.

Methods

The American College of Physicians' Population Health and Medical Science Committee (PHMSC) developed this best practice advice. In areas where evidence is uncertain or emerging or practice does not follow the evidence, the PHMSC educates and provides clinical advice to internal medicine physicians and other clinicians of best practice based on a review and assessment of available scientific work, such as available clinical guidelines, systematic reviews, and individual studies. The search described in **Table 1** identified the following sources of evidence for the PHMSC's advice: an Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center living systematic review on the benefits and harms of cannabis for chronic noncancer pain (2024 update) (29, 30); the Systematically Testing the Evidence on Marijuana series of living systematic and narrative reviews) (31); and additional evidence reviews and clinical guidance statements as referenced in this article. The AHRQ review is the source of the certainty of evidence ratings for benefits and short-term harms (29). The marked variation in costs across the different cannabis products people use to manage chronic pain prohibited the consideration of costs in the development of this best practice advice (32).

Benefits and Harms of Cannabis or Cannabinoids for Chronic Noncancer Pain

Overview

As of September 2024, the AHRQ living systematic review identified 26 randomized controlled trials (RCTs) and 12 observational studies examining the effects of cannabis or cannabinoids on chronic noncancer pain compared with placebo or usual care (see **Figure 1** for a summary of findings) (29). The treatment or follow-up duration in the RCTs ranged from 4 to 47 weeks. Most of the RCTs (19 of 26) were conducted in populations with neuropathic pain; other conditions studied were fibromyalgia, osteoarthritis, temporomandibular pain, inflammatory arthritis, musculoskeletal pain, headache, visceral pain, and unspecified chronic pain.

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Table 1. Search Strategy

Databases searched	
	Ovid MEDLINE
Additional sources	
	American Society of Regional Anesthesia and Pain Medicine
	Canadian Medical Association
	DynaMed
	Emergency Care Research Institute Guidelines Trust
	Guidelines International Network
	Michael G. DeGroote Centre for Medicinal Cannabis Research
	National Council of State Boards of Nursing
	National Institute for Health and Care Excellence
	Scottish Intercollegiate Guidelines Network
	UpToDate
	Veterans Affairs/Department of Defense Clinical Practice Guidelines
Keywords	
	Cannabis, marijuana, hashish, hash, ganja, hemp, bhang, charas, endocannabinoid, phytocannabis, CBD, THC, and variations on these words

CBD = cannabidiol; THC = delta-9-tetrahydrocannabinol.

The evidence about benefits and short-term harms was obtained in both men (42% of participants) and women (58% of participants) and is most applicable to middle-aged patients (average age across the studies was 54 years) with moderate to severe neuropathic pain (the average pain score at the beginning of the RCTs was 6.6 on a 0- to 10-point scale, ranging from 4.0 to 8.67). There was poor representation of people of color and those with serious mental illness or other comorbidities. Patients may have been taking other medications for chronic noncancer pain before and during the studies.

Benefits: Pain and Function Outcomes

The 2 most-studied cannabinoid formulations are a whole plant–derived oromucosal spray containing comparable amounts of THC and CBD called nabiximols (not U.S. Food and Drug Administration–approved for use or available in the United States) and synthetic THC preparations with a high THC–CBD ratio.

There is moderate-certainty evidence that nabiximols probably improve chronic noncancer pain severity and function or disability to a small degree. The mean daily dose across these trials was 23 mg of THC and 21 mg of CBD after titration.

There is low-certainty evidence that synthetic or purified THC preparations with a high THC–CBD ratio may improve chronic noncancer pain severity to a small degree but may have no effect on function or disability. The mean dose used in these RCTs is more difficult to summarize given the different synthetic preparations used across studies, but the daily dose of dronabinol (a synthetic form of THC) ranged from 13 to 25 mg of THC across 4 RCTs after titration, similar to total daily THC doses evaluated in comparable THC–CBD ratio oromucosal spray studies.

There is moderate-certainty evidence that synthetic or purified oral CBD alone with a low THC–CBD ratio probably has no effect on pain response, pain severity, and function or disability. There is low-certainty evidence that combined oral purified THC and synthetic CBD with a low THC–CBD ratio (in an approximate 1:2 ratio) may have no effect on pain response, pain severity, and function or disability.

There is insufficient evidence to draw conclusions about the benefits of other cannabinoid preparations, including whole plant cannabis, topical CBD, and other cannabinoids, as well as comparisons with active noncannabis treatments or between cannabis-related products.

Short-Term Harms

Evidence showed cannabis formulations with comparable THC and CBD (the whole plant–derived oromucosal spray nabiximols) may result in a large increased risk for dizziness and sedation and a modest increased risk for nausea (low-certainty evidence). However, this formulation may not increase the rate of study withdrawal due to adverse events (low-certainty evidence).

The synthetic or purified THC preparations with a high THC–CBD ratio probably result in a large increase in the risk for dizziness (moderate-certainty evidence) and may result in a large increase in nausea and a modest increase in the risk for sedation and rate of study withdrawal due to adverse events (low-certainty evidence). Of note, frail populations who may be at increased risk for more serious consequences from dizziness and sedation have not been adequately studied.

There is low-certainty evidence that synthetic or purified oral CBD alone with a low THC–CBD ratio may not result in increased dizziness and sedation. There is moderate-certainty evidence that combined oral purified THC and synthetic CBD with a low THC–CBD ratio probably results in a large increase in nausea and low-certainty evidence that this formulation may result in a modest increase in dizziness and sedation.

There is insufficient evidence to draw conclusions about the short-term harms of other cannabinoid preparations, including whole plant cannabis, topical CBD, and other cannabinoids.

Long-Term Harms

The trials included in the AHRQ living systematic review (29) described earlier were too small and brief to be informative about the risks for adverse effects that may accrue over months to years. Table 2 summarizes important findings from other research about harms, including cannabis use disorder, cannabis withdrawal syndrome, and cognitive effects, as well as cardiovascular, gastrointestinal, and pulmonary effects and pregnancy-related harms (33–61).

BEST PRACTICE ADVICE

The intended audience for this advice is clinicians caring for patients with chronic noncancer pain who have had other evidence-based treatments fail and are considering cannabis or cannabinoids.

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Figure 1. Summary of benefits and short-term harms of cannabis or cannabinoids for chronic noncancer pain (primarily neuropathic).

Product *Average Daily Dose*	Outcomes*							
	Benefits			Short-Term Harms				
	Pain Response†	Pain Severity‡	Function or Disability‡	Withdrawal due to AEs	SAEs	Dizziness	Nausea	Sedation
Comparable THC-CBD ratio§ vs. placebo or usual care								
Whole plant–derived, oral spray *23 mg of THC and 21 mg of CBD*	38% vs. 31% RR 1.18 (95% CI, 0.93 to 1.71) ●○○	MD −0.54 (CI, −0.95 to −0.19) ●●○	MD −0.42 (CI, −0.73 to −0.16) ●●○	12.5% vs. 10.2% RR 1.14 (CI, 0.65 to 3.02) ●○○	5.0% vs. 4.3% RR 1.18 (CI, 0.26 to 3.4) ●○○	31% vs. 8.0% RR 3.57 (CI, 2.42 to 5.60) ●○○	14% vs. 7.5% RR 1.79 (CI, 1.19 to 2.77) ●○○	8.0% vs. 1.2% RR 5.04 (CI, 2.10 to 11.89) ●○○
Interpretation	↑ May result in a small improvement	↓ Probably results in a small improvement	↓ Probably results in a small improvement‖	↔ May be no difference	↔ May be no difference	↑ May result in a large increase	↑ May result in a medium increase	↑ May result in a large increase
High THC-CBD ratio¶ vs. placebo or usual care								
Synthetic or purified, oral *13 to 25 mg of THC*	Insufficient ○○○	MD −0.78 (CI, −1.59 to −0.08) ●○○	MD −0.18 (CI, −1.25 to 0.77) ●○○	14% vs. 7% RR 1.92 (CI, 1.10 to 4.80) ●○○	Insufficient ○○○	33% vs. 15% RR 2.30 (CI, 1.53 to 3.52) ●●○	12% vs. 6% RR 2.12 (CI, 1.09 to 3.96) ●○○	24% vs. 16% RR 1.57 (CI, 1.11 to 2.29) ●○○
Interpretation	? Uncertain	↓ May result in a small improvement	↔ May be no difference	↑ May result in a medium increase	? Uncertain	↑ Probably results in a large increase	↑ May result in a large increase	↑ May result in a medium increase
Whole plant–extracted, oral or sublingual *4.4 mg of THC and 0.08 mg of CBD or max daily THC dose of 25 mg*	No evidence	Insufficient ○○○	Insufficient ○○○	13.9% vs. 5.7% RR 3.12 (CI, 1.54 to 6.33) ●○○	Insufficient ○○○	62.2% vs. 7.5% RR 8.34 (CI, 4.53 to 15.34) ●○○	No evidence	No evidence
Interpretation	No evidence	? Uncertain	? Uncertain	↑ May result in a large increase	? Uncertain	↑ May result in a large increase	No evidence	No evidence

Data are based on the Agency for Healthcare Research and Quality living systematic review (29). AE = adverse event; CBD = cannabidiol; CBDV = cannabidivarin; MD = mean difference on a 0 to 10 scale; RR = relative risk; SAE = serious adverse event; SMD = standardized mean difference; THC = delta-9-tetrahydrocannabinol.

* Magnitude of effect is categorized as small, medium, or large based on preset thresholds in the Agency for Healthcare Research and Quality living systematic review. Unless otherwise noted, results below the threshold for a small effect were considered to reflect no effect (29). Color coding: green = desirable effect; red = undesirable effect. Certainty of evidence: ○○○ = insufficient, the true result is likely very different from what was observed and any conclusion is uncertain; ●○○ = low, the true result might be very different from what was observed and additional studies probably will change conclusions; ●●○ = moderate, the true result is probably close to what was observed but additional studies might change conclusions; ●●● = high, the true result is very close to what was observed and additional studies would not change conclusions.

† Defined as ≥30% improvement in pain (29).

‡ Negative values indicate improved pain severity or function or disability (29).

§ THC–CBD ratio is <2:1 and >1:2 (29).

‖ Improvement in overall function favored the cannabis product but was slightly below the threshold for small (29).

¶ THC–CBD ratio is ≥2:1 (29).

** THC–CBD ratio is <1:2 (29).

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Figure 1–Continued.

Low THC-CBD ratio vs. placebo or usual care**								
Synthetic or purified CBD alone, oral *30 to 600 mg of CBD*	37.0% vs. 44.4% RR 0.84 (CI, 0.62 to 1.10) ●●○	MD 0.40 (CI, −0.15 to 1.00) ●●○	SMD 0.11 (CI, −0.14 to 0.41) ●●○	Insufficient ○○○	Insufficient ○○○	13.3% vs. 18.5% RR 0.75 (CI, 0.28 to 1.81) ●○○	Insufficient ○○○	16.3% vs. 19.4% RR 1.07 (CI, 0.21 to 1.93) ●○○
Interpretation	↔ Probably no difference	↔ Probably no difference	↔ Probably no difference	? Uncertain	? Uncertain	↔ May be no difference	? Uncertain	↔ May be no difference
Combined purified and synthetic CBD, oral *22.5 to 25 mg of THC and 45 to 50 mg of CBD*	55.2% vs. 50.8% RR 1.07 (CI, 0.73 to 1.57) ●○○	MD 0.12 (CI, −0.71 to 0.93 ●○○	SMD 0.29 (CI, −0.21 to 0.80) ●○○	Insufficient ○○○	Insufficient ○○○	35.1% vs. 23.1% RR 1.74 (CI, 0.47 to 3.46) ●○○	24.1% vs. 6.2% RR 3.80 (CI, 1.08 to 17.05) ●●○	43.1% vs. 29.2% RR 1.55 (CI, 0.86 to 2.72) ●○○
Interpretation	↔ May be no difference	↔ May be no difference	↔ May be no difference	? Uncertain	? Uncertain	↑ May result in a medium increase	↑ Probably results in a large increase	↑ May result in a medium increase
Products with uncertain and/or lacking evidence								
Low THC-CBD ratio	Extracted CBD, topical; sublingual CBD/THC, extracted; intraoral (topical) CBD, unclear if synthetic or plant-derived							
Other cannabinoids	Oral CBDV; whole plant cannabis (12% THC)							

Best Practice Advice 1a: Clinicians should counsel patients about the benefits and harms of cannabis or cannabinoids when patients are considering whether to start or continue to use cannabis or cannabinoids to manage their chronic noncancer pain.

Best Practice Advice 1b: Clinicians should counsel the following subgroups of patients that the harms of cannabis or cannabinoid use for chronic noncancer pain are likely to outweigh the benefits: young adult and adolescent patients, patients with current or past substance use disorder, patients with serious mental illness, and frail patients and those at risk for falling.

Best Practice Advice 2: Clinicians should advise against starting or continuing to use cannabis or cannabinoids to manage chronic noncancer pain in patients who are pregnant or breastfeeding or actively trying to conceive.

Best Practice Advice 3: Clinicians should advise patients against the use of inhaled *cannabis to manage chronic noncancer pain.*

Rationale for Best Practice Advice Statements

In most U.S. states, patients will obtain cannabis for chronic pain through a dispensary. However, clinicians are best positioned to provide evidence-based information about the benefits and harms most relevant to an individual patient's needs and comorbidities to enable patients to make informed decisions about starting or continuing cannabis or cannabinoid use for chronic noncancer pain.

For many patients, the current evidence suggests that the harms of cannabis and cannabinoid use to manage chronic noncancer pain outweigh the small potential benefits. Evidence shows that in patients primarily with chronic noncancer neuropathic pain, a cannabis formulation with comparable THC–CBD ratio probably results in small improvements in pain severity (approximately 0.5 to 1.0 points on a 0- to 10-point numerical rating scale) and function or disability (approximately 0.4-point improvement on a 0- to 10-point numerical rating scale). However, the evidence is insufficient to show benefit for other types of chronic noncancer pain. High THC–CBD ratio synthetic or purified products may result in small improvements in pain severity (approximately 0.5- to 1.0-point improvement on 0- to 10-point numerical rating scale) but no change in overall function or disability.

Chronic noncancer pain is often managed for many years and, although cannabis and cannabinoid treatment trials have identified several short-term harms that are important to counsel patients about (see Figure 1), few trials have examined outcomes beyond several months. Evidence is limited but suggests various long-

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Table 2. Summary of Long-Term Harms of Cannabis and Cannabinoid Use

Long-Term Harm	Evidence Source	Finding
Cannabis use disorder	Systematic review (33) Cohort study (34) *Diagnostic and Statistical Manual of Mental Disorders* (35)	U.S. prevalence: 10% to 30% of those reporting past-year cannabis use (33) Symptoms: characterized by tolerance, withdrawal, and an increasing amount of time spent in activities related to cannabis use, often at the expense of fulfilling one's responsibilities in those with more severe cannabis use disorder (35) Risk factors: prevalence is higher among adolescents and young adults, males, those with a history of substance use disorder and/or psychiatric disorder, and those that use cannabis more frequently and over longer periods of time (33, 34)
Cannabis withdrawal syndrome	Systematic review (36)	U.S. prevalence: 17% to 87%, depending on setting (47% overall) (36) Symptoms: anxiety, irritability, and insomnia and start 24 to 48 h after stopping cannabis use, peaking during days 2 to 6 after cessation, and lasting up to 3 wk among those who use cannabis daily or near daily (36) Risk factors: concurrent tobacco or other substance use and daily cannabis use are associated with a higher prevalence (36)
Cognitive effects		
Acute effects	Systematic review (37) Narrative reviews (38, 39)	Acute cannabis intoxication is associated with mild to moderate effects on verbal learning, verbal memory, working memory, executive functioning, and processing speed (37, 39) There is likely a dose-response effect related to THC dose (38)
Chronic effects	Systematic reviews (40, 41) Narrative reviews (38, 39)	Adolescents who use cannabis regularly may experience small declines in IQ (38, 41) Clinically significant cognitive effects may largely resolve after abstinence, although the influence of factors such as duration of cannabis use and duration of abstinence is unclear (38–40)
Mental health effects		
Acute psychosis	Systematic review (42)	Large amounts of THC consumption can induce acute psychosis, which can sometimes be severe enough to require hospitalization (42)
Psychotic spectrum disorders	Case–control study (43) Cohort studies (44, 45) Cross-sectional study (46)	May be associated with long-term use of cannabis, particularly with use of high potency cannabis and with use starting at younger ages (43) Increased rates and earlier onset may be associated with early and heavy cannabis use in those with developing brains (44, 45) Association is particularly pronounced among those with a genetic predisposition to psychotic spectrum disorders (46)
Bipolar type 1 disorder	Systematic review (47)	Association of cannabis use with an increased incidence of mania in those with bipolar type I disorder (47)
Physical health effects		
Cancer	Systematic review (48) Cohort study (49)	Unclear whether cannabis increases risk for most types of cancer, including lung, head and neck, prostate, and colorectal cancer, although studies are limited by small populations of cannabis-only users (48) Low-certainty evidence of increased risk for testicular germ cell tumors with >10 y of cannabis use (48) One study found those with cannabis use disorder had a higher risk for head and neck cancer (49)
Cardiovascular	Narrative review (50) Case-crossover study (51) Cohort studies (52, 53) Cross-sectional study (54)	Cannabis use is associated with tachycardia, hypertension, and postural hypotension (50, 51) Cannabis can induce angina in high-risk persons, but unclear association with myocardial infarction, stroke, or atrial fibrillation particularly in lower-risk persons (52–54)
Gastrointestinal	Systematic review (55) Narrative review (56)	Cannabinoid hyperemesis syndrome (form of cyclical vomiting syndrome) occurs in some regular cannabis or cannabinoid users (55, 56)
Pregnancy	Systematic review (57)	Cannabis use during pregnancy has been associated with increased risk for adverse neonatal outcomes, including preterm birth, small for gestational age births, and perinatal mortality (57)
Pulmonary	Systematic review (58) Literature review (59) Cohort studies (60, 61)	Regular cannabis use is associated with bronchitis (58, 59) Unclear association between cannabis use and chronic obstructive pulmonary disease, particularly in lower-risk populations who do not use cannabis heavily (58–60) Unclear association between cannabis use and the risk for lung cancer (59, 61)

IQ = intelligence quotient; THC = delta-9-tetrahydrocannabinol.

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Figure 2. Discussion points with patients who are considering cannabis or cannabinoids to manage their chronic noncancer pain.

The degree of benefit to ease chronic noncancer pain is, on average, small. We do not know how effective cannabis or cannabinoids are for pain over years of use. The potential benefits of cannabis for chronic noncancer pain should be weighed against the known short-term and long-term harms. Most people should try other treatment options before trying cannabis or cannabinoids for the management of chronic noncancer pain.

It is difficult to apply what we know from studies to practice in the United States because the potency (THC content) of products in dispensaries is typically far higher than that used in studies and because cannabis flower has not been well studied. Many of the harms associated with cannabis and cannabinoids are related to the total amount of THC used. It is best to use the least amount of THC necessary to achieve a beneficial effect.

The best studied form of cannabis is nabiximols, an oromucosal spray that delivers 2.7 mg of THC and 2.5 mg of CBD per spray and is not currently available in the United States. In studies, patients began with 1 spray and increased as needed to an average of 8 sprays per day over several weeks. The average effective daily dose of THC in these studies, and in studies of oral synthetic THC, was about 15–25 mg of THC per day.

If cannabis or cannabinoids are used for chronic noncancer pain, start at a low dose. There are several expert-based guidelines outlining titration strategies (77–79).

The goal of any treatment for chronic pain is to improve patients' ability to do the things they want and need to do. Establish and review functional goals at the outset. Stop using cannabis or cannabinoids if it is not helping to improve function or if it is causing adverse effects that outweigh the benefit experienced.

A patient should keep a record of their daily cannabis or cannabinoid use, including dose and timing, the effect on their chronic noncancer pain and their ability to do things, and any adverse effects.

Do not drive after using cannabis or cannabinoids. Be aware that some workplaces may test for drug use (including cannabis and cannabinoids) and that smoking cannabis can affect others through secondhand smoke.

Cannabis and cannabinoids can be addictive, even if it is being used to manage chronic noncancer pain. Some signals that show a patient may be developing problems with cannabis or cannabinoid use include the development of

- **tolerance (needing more cannabis to get the same effect);**
- **withdrawal (experiencing symptoms like irritability or insomnia when stopping or reducing cannabis use); or**
- **effects on social, professional, or mental well-being, such as relationship problems, forgoing activities in favor of using cannabis, failing to fulfill obligations, and continuing to use even if a patient feels it is causing physical or psychological problems.**

CBD = cannabidiol; THC = delta-9-tetrahydrocannabinol.

term harms, with some patients at higher risk for these harms (Table 2).

Adolescents (aged 10 to 19 years per the World Health Organization) (62) and young adults (up through age 25 years) are particularly vulnerable to the adverse effects of regular, long-term cannabis use on the developing brain. These effects include adverse cognitive effects (63)—especially from ongoing cannabis use—as well as a higher rate of psychotic symptoms and a higher incidence and earlier onset of psychotic spectrum disorders (43, 64–66). Adolescents and young adults who use cannabis are also at a higher risk for developing cannabis use disorder than older patients (33, 67). Although cannabis in low doses seems to be anxiolytic, high doses can worsen anxiety (68). Young adults with mood disorders and those who use high-potency cannabis (that is, with high THC content) are particularly at high risk for cannabis use disorder and serious adverse mental health effects associated with cannabis use disorder (69, 70). Similarly, patients with current or past substance use disorders are at higher risk for the development of cannabis use disorder (33, 34).

Patients with serious mental illness are at risk for adverse mental health effects of cannabis in several ways. There is consistent evidence that cannabis use is associated with an increased incidence of mania in patients with bipolar I disorder (47). In patients with psychotic spectrum disorder, cannabis use increases the burden of psychotic symptoms (71). Although the long-term effects of cannabis and cannabinoids on patients with depression and anxiety are unclear (72), there is evidence that high doses of THC can acutely induce anxiety and depression symptoms (42), which may be important to consider when counseling patients with anxiety and depression.

As outlined in Figure 1, all THC-containing products (those with high, comparable, and low THC–CBD ratios) can increase the risk for dizziness and sedation. In frail patients, who may also be taking other centrally acting medications, and those who are at high risk for falling, cannabis may increase fall and injury risk, suggesting that the harms of cannabis use for chronic noncancer pain likely outweigh the benefits in this group (73).

Cannabis use during pregnancy has been associated with adverse neonatal outcomes (33, 57). After controlling for confounders, including tobacco use, cannabis use during pregnancy is associated with an increased risk for preterm birth (adjusted odds ratio across 12 studies, 1.42 [95% CI, 1.19 to 1.69]; low-certainty evidence), an increased risk for small for gestational age births (adjusted odds ratio across 6 studies, 1.76 [CI, 1.52 to 2.05]; low-certainty evidence), and an increased risk for perinatal mortality (adjusted odds ratio across 5 studies, 1.50 [CI, 1.39 to 1.62], very low–

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certainty evidence). Relatively little is known about the clinical effects of cannabis use while breastfeeding, but THC is known to transfer into human milk and theoretically could adversely affect the rapidly developing infant brain (74).

Observational studies have not established whether cannabis smoking is an independent risk factor for chronic obstructive pulmonary disease but have mostly enrolled lower-risk populations who do not use cannabis heavily (58–60). However, there are several reasons to counsel patients against inhaled cannabis as the predominant route of administration for chronic noncancer pain management. First, cannabis smoke involves the same mechanism of combustion and contains many of the same toxins and carcinogens as tobacco smoke. Second, regular cannabis use is associated with symptoms of chronic bronchitis (58, 59). Third, there are no long-term studies examining the safety of heavy, long-term use of inhaled cannabis nor of the safety of inhaled use in older patient populations and those with existing lung disease. Studies have not shown that cannabis smoking increases the risk for lung cancer, but these studies are limited because many participants also smoked tobacco, the levels of cannabis use were relatively low, and cannabis was less potent at the time of the studies (48). Of note, although prior studies have not established whether cannabis smoking increases the risk for head and neck cancer, a recent study found that participants with cannabis use disorder—who presumably used cannabis heavily—had a 2.5- to 8-fold higher risk for head and neck cancer (49).

Whereas cannabis smoking is associated with the risks noted earlier, edibles can be associated with short-term harms from accidental ingestion of high doses, particularly in cannabis-naive patients who may not realize edibles take 1 to 2 hours to produce a noticeable effect (75). The oral metabolite of THC, 11-OH-THC, is more potent than THC and may also contribute to overdose. Although overdoses are not fatal, they can lead to emergency department visits and, occasionally, hospitalization for symptoms such as anxiety, panic attacks, and acute psychosis (76).

Clinical Considerations

Figure 2 provides discussion points for clinicians counseling patients who are considering use of cannabis to manage chronic noncancer pain. It is important for clinicians to frame conversations about cannabis use within the context of failure of other evidence-based therapeutic options (77–79).

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Acknowledgment: ACP staff who participated in the development of this project but did not vote or author: Kate Carroll, MPH, and Curtis S. Harrod, PhD, MPH.

Financial Support: Financial support for the development of this best practice advice comes exclusively from the ACP operating budget.

Disclosures: All financial and intellectual disclosures of interest were declared, and potential conflicts were discussed and managed. Dr. Kansagara was recused from voting due to a moderate-level conflict of interest (recently authored publications). A record of disclosures of interest and management of conflicts is kept for each Population Health and Medical Science Committee meeting and conference call and can be viewed at www.acponline.org/about-acp/who-we-are/leadership/boards-committees-councils/population-health-and-medical-science-committee/doi-and-coi-management-summary-for-population-health-and-medical-science-committee. Disclosure forms are available with the article online.

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