

Julius Metts, MD, FAAFP; Steven Wright, MD, FAAFP; Jawahar Sundaram, MD; Nastran Hashemi, MD

California Substance Abuse and Treatment Center, Department of Corrections and Rehabilitation, Corcoran (Drs. Metts, Sundaram, and Hashemi); Private practice, Littleton, Colo (Dr. Wright)

julius.metts@cdcr.ca.gov

The authors reported no potential conflict of interest relevant to this article.

Medical marijuana: A treatment worth trying?

With medical marijuana available in more and more states, family physicians need to know what the evidence says about its use. This review includes a step-by-step guide and a list of red flags to watch for.

PRACTICE RECOMMENDATIONS

› Consider recommending medical marijuana for conditions with evidence supporting its use only after other treatment options have been exhausted. **(B)**

› Thoroughly screen potential candidates for medical marijuana to rule out a history of substance abuse, mental illness, and other contraindications. **(C)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶ Gladys B, a 68-year-old patient with a history of peripheral neuropathy related to chemotherapy she underwent years ago, has been treated alternately with acetaminophen with codeine, tramadol, gabapentin, and morphine. Each provided only minimal relief. Your state recently legalized medical marijuana, and she wants to know whether it might alleviate her pain.

If Ms. B were your patient, how would you respond?

Medical marijuana is now legal in 23 states and Washington, DC. Other states are considering legalization or have authorized particular components for use as medical treatment.¹ As such laws proliferate and garner more media attention, it is increasingly likely that patients will turn to their primary care physicians with questions about the use of marijuana for medicinal purposes. What can you tell them?

Conversations about medical marijuana should be based on the understanding that while many claims have been made about the therapeutic effects of marijuana, only a few of these claims have evidence to back them up. Major medical organizations, including the American Academy of Family Physicians,² the American College of Physicians,³ and the Institute of Medicine,⁴ recognize its potential as a treatment for various conditions, but emphasize the need for additional research rather than wholesale adoption.

Most commonly, medical marijuana is used to treat pain symptoms, but it is also used for a host of other conditions. A 2015 systematic review and meta-analysis⁵ found moderate-quality evidence to support its use for the treatment of chronic and neuropathic pain and spasticity associated with multiple sclerosis (MS), and low-quality evidence for the treatment of nausea and vomiting associated with chemotherapy, for



Recommend marijuana only after standard medications, including FDA-approved cannabinoids, and nonpharmaceutical approaches have proven inadequate.

weight gain in patients with human immunodeficiency virus (HIV), and to treat Tourette syndrome. (TABLE 1 lists the conditions for which medical marijuana has been found to be indicated.⁵⁻¹³) For most other conditions that qualify for the use of medical marijuana under state laws, however—insomnia, hepatitis C, Crohn’s disease, and anxiety and depression, among others—the evidence is either of very low quality or nonexistent.⁵

Evaluating marijuana is difficult

It is important to note that marijuana comprises more than 60 pharmacologically active cannabinoids, which makes it difficult to study. Both exogenous ligands, such as the cannabinoids from marijuana, and endogenous ligands (endocannabinoids), such as anandamide and 2-arachidonoylglycerol, act on cannabinoid receptors. These receptors are found throughout the body, but are primarily in the brain and spinal cord.¹⁴

The main cannabinoids contained in marijuana are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC produces the euphoria for which recreational marijuana is known, but can also induce psychosis. CBD is not psychoactive and is thought to have antianxiety and possibly antipsychotic properties. Thus, marijuana’s

therapeutic effects depend on the concentration of THC in a given formulation. Because CBD has the ability to mitigate psychoactive effects, the ratio of THC to CBD is important, as well.¹⁵

What’s more, medical marijuana is available in various forms. It can be smoked—the most widely used route—or inhaled with an inhalation device, ingested in food or as a tea, taken orally, administered via an oromucosal spray, or even applied topically. Medical marijuana may be extracted naturally from the cannabis plant, produced by the isomerization of CBD, manufactured synthetically, or provided as an herbal formulation.

There are also cannabinoids that have been approved by the US Food and Drug Administration (FDA)—dronabinol (a synthetic version of THC) and nabilone (a synthetic cannabinoid). Nabiximols, a cannabis extract in the form of an oromucosal spray, is licensed in the UK for the treatment of symptoms associated with multiple sclerosis, but has not yet received FDA approval.^{16,17}

As with any treatment or medication, the benefits must be weighed against the risks. Scientific studies have documented many adverse health effects associated with marijuana, including the risk of addiction and the potential for marijuana to be used as a gateway drug; its effect on brain development,

IMAGE: © JOE GORMAN



INSTANT POLL

Have you ever recommended medical marijuana for a patient?

- Yes
- No

jfponline.com

➤
Marijuana's therapeutic effects depend on the concentration of THC in a formulation and on the ratio of THC to cannabidiol.

TABLE 1
Indications for medical marijuana⁵⁻¹³

| Condition/symptom | SOR |
|---|-----|
| Spasticity/pain in MS | B |
| Neuropathic, cancer, and chronic pain | B |
| Tourette syndrome | C |
| Insomnia | C |
| CINV for breakthrough symptoms | C |
| Cachexia in HIV (if first-line medications are not effective) | C |

CINV, chemotherapy-induced nausea and vomiting; HIV, human immunodeficiency virus; MS, multiple sclerosis; SOR, strength of recommendation.

school performance, and lifetime achievement; a potential relationship to mental illness; and the risk of cancer and motor vehicle accidents.^{1,16,18} Patients in clinical trials have reported dizziness, dysphoria, hallucinations, and paranoia, as well.¹²

What's more, marijuana remains classified as a Schedule I agent.¹⁹ Because of its high potential for abuse, physicians in states where medical marijuana has been legalized should adhere to off-label prescribing principles: Recommend it only after standard medications, including FDA-approved cannabinoids, and nonpharmaceutical approaches have proven to be inadequate.^{6,20,21}

Medical marijuana for your patient? A look at the evidence

The meta-analysis cited earlier included 79 randomized clinical trials (RCTs) of medical marijuana used for a variety of conditions in a number of delivery modes. However, only 4 were judged to be of low risk of bias.⁵ Nonetheless, here's a look at this and other evidence.

Chronic and neuropathic pain

Twenty-eight of the 79 studies addressed chronic pain, with half assessing the oromucosal spray (nabiximols). Most others studied marijuana that was smoked or inhaled. Neuropathic pain was most frequently studied, but cancer pain, fibromyalgia, and musculoskeletal pain, among others, were also evaluated.⁵

The average number of patients who

reported a reduction in pain of $\geq 30\%$ was greater with marijuana compared with placebo (odds ratio=1.41; 95% confidence interval, .99-2.0). Delivery mode did not affect outcomes; different forms of administration were not associated with any significant difference in pain relief. Nor were there significant differences in results among the various pain conditions studied. Notably, however, quality of life measurements did not reflect any overall improvement.⁵

The authors of a literature review of marijuana for chronic and neuropathic pain and MS-induced spasticity did find high-quality evidence of its efficacy in several of the trials they assessed.⁶ And a review of well-conducted observational trials of smoked marijuana as a treatment for severe neuropathic pain revealed that it may be indicated for those who fail to respond to FDA-approved cannabinoids and standard analgesics.¹⁰ Neither functional status nor quality of life was evaluated, however, and none of the observational studies compared smoked cannabis to standard analgesics.

Notably, the authors did not recommend smoked marijuana for pain conditions such as low back pain and fibromyalgia, which are commonly seen in practice. That's because the safety and efficacy of smoked cannabis has not been studied for these conditions and because evidence-based treatments for these disorders exist.¹⁰

CASE ▶ Before considering medical marijuana for Ms. B, you suggest a trial of dronabinol. The patient agrees, and you prescribe

2.5 mg twice a day. You schedule a visit in 4 weeks to review the drug's efficacy and tell her to call if she develops psychiatric symptoms, such as hallucinations or paranoia, or impaired cognition. You also advise her that dronabinol may increase the risk of auto accidents and caution her to avoid driving for 6 hours after taking the drug—or longer if she experiences an initial “high.”

MS symptoms

A comprehensive review of medical marijuana studies spanning nearly 7 decades revealed 12 trials focusing on MS—and found its use in treating MS-related spasticity supported by high-quality evidence.⁶

Two of the largest studies were done in the UK.^{7,8} One multicenter trial included 630 participants randomized to treatment with an oral cannabinoid extract, THC, or placebo for 6 weeks.⁷

There was no change in the primary outcome measure, the Ashworth spasticity scale. However, there was a treatment effect on patient-reported spasticity and pain, with improvement in spasticity reported by 61% of those treated with the cannabinoid extract, 60% of those treated with THC, and 46% of those treated with placebo.⁷

The other UK trial involved 22 centers and 279 patients, randomized to either oral cannabis extract or placebo. The primary outcome measure involved a category rating scale that reported on change in muscle stiffness since baseline and on body pain, spasms, and sleep quality. This study used a 2-week titration phase and a 10-week maintenance phase. The rate of relief from muscle stiffness after 12 weeks was almost twice as high in the cannabis extract group (29%) compared with placebo (16%).⁸

A systematic review of the efficacy and safety of medical marijuana by the American Academy of Neurology (AAN) concluded that oral cannabis extract, THC, and nabiximols are “probably effective” in reducing patient-centered measures of spasticity and pain associated with MS.⁹

■ **Little help for other neurologic disorders.** Studies of the efficacy and safety of medical marijuana for other neurologic disorders have been less encouraging. The AAN

concluded that cannabinoids are probably ineffective for the treatment of tremors, and that oral cannabis extract is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson's disease.

A 2014 systematic review found that oral cannabinoids were of unknown efficacy in treating nonchorea-related symptoms of Huntington's disease, Tourette syndrome, cervical dystonia, and epilepsy.⁹ The 2015 systematic review and meta-analysis cited earlier, however, suggests that there is low-quality evidence that cannabinoids improve symptoms associated with sleep disorders and Tourette symptoms.⁵

Cancer-related symptoms

In 1985, the FDA approved dronabinol for the treatment of chemotherapy-induced nausea and vomiting (CINV) not controlled by other medications. Nabilone followed, receiving FDA approval in 1992.¹¹

Serotonin receptor antagonists (5-HT₃ receptor antagonists) were also introduced in the early 1990s. In 2001, a systematic review of 30 RCTs with a total of 1366 patients looked at how cannabinoids—including oral dronabinol, oral nabilone, and intramuscular levonantradol, a synthetic drug that does not have FDA approval—compared with placebo or other antiemetics.¹²

The researchers found the FDA-approved cannabinoids to be more effective than prochlorperazine, metoclopramide, chlorpromazine, and other antiemetics for most patients. (The included studies did not compare cannabinoids with 5-HT₃ agents.) That was not the case, however, for patients receiving either very low or very highly emetogenic chemotherapy.

In crossover studies, participants reported that they preferred cannabinoids for future CINV control. Although they cited the “high,” sedation, and euphoria as potential beneficial effects, those taking cannabinoids were also more likely than patients receiving other antiemetics to withdraw from studies due to adverse effects, including dizziness, dysphoria, depression, hallucinations, and paranoia. The authors concluded that cannabinoids might be useful as mood-enhancing adjuvants for controlling CINV, but that



Those taking cannabinoids were more likely than patients taking other antiemetics to withdraw from studies due to adverse effects, such as dizziness and hallucinations.

➤ **Vaporization of marijuana may eliminate some of the irritating—and possibly carcinogenic—substances contained in marijuana smoke.**

short-term adverse effects were likely to limit their widespread use.¹²

Recommended antiemetic regimens for patients with highly emetogenic regimens or those whose chemotherapy comes with a high risk of delayed CINV include the serotonin antagonist dexamethasone, with or without aprepitant or fosaprepitant. Because of the availability of safer and more effective agents, the National Comprehensive Cancer Network (NCCN) does not consider cannabinoids first-line treatment for the prevention of CINV. Instead, they are reserved for breakthrough symptoms or refractory nausea and vomiting.¹¹

In fact, NCCN practice guidelines do not recommend medical marijuana for the management of CINV because of both medical and legal concerns. Even in states in which medical marijuana is legal, the organization states, its use is controversial.¹¹

■ Combatting anorexia and cachexia.

An estimated 50% of cancer patients develop anorexia and cachexia. The systemic inflammation and loss of protein, energy, and lean body mass is associated not only with a poor response to chemotherapy and decreased survival rates, but also with a lower quality of life. While therapies to alleviate these symptoms typically focus on palliation and reduction of distress rather than on prolonging life, some agents, such as megestrol and medroxyprogesterone, are reported to improve survival rates as well as quality of life.²²

Cannabinoids have also been used to increase appetite and food intake and facilitate weight gain in cancer patients. The exact mechanism by which this effect occurs is not known; in fact, questions about the extent of the effect itself remain.

Two RCTs failed to show benefits in this regard compared with megestrol or placebo. One study of 469 patients with advanced cancer compared dronabinol, administered alone or in combination with megestrol, with megestrol alone. Using a Functional Assessment of Anorexia/Cachexia Therapy Questionnaire to assess quality of life, the researchers found that megestrol provided better palliation of anorexia than dronabinol alone and that the combination of dronabinol and megestrol showed no advantage over megestrol alone.¹³

The second study was a multicenter Phase III double-blind RCT comparing cannabis extract (CE), THC, and placebo in 289 cancer patients. The researchers found no differences in appetite, quality of life, or toxicity among those in the 3 arms of the study. A data review board subsequently recommended that study recruitment be stopped because of the absence of significant differences.²³

HIV and AIDS-related morbidity and mortality

Evidence of the efficacy and safety of cannabinoid use among adult patients with HIV or acquired immune deficiency syndrome (AIDS) is lacking, according to a 2013 Cochrane review.²⁴ The review looked at RCTs that compared any marijuana intervention in this patient population to either placebo or a known treatment, such as megestrol or medroxyprogesterone. Worth noting, however, is that the review included studies that were of short duration, involved small numbers of patients, and focused on short-term measures of efficacy.

Long-term studies indicating that cannabinoids have a sustained effect on AIDS-related morbidity and mortality in patients being treated with antiretroviral therapy have yet to be conducted.²⁴ The systematic review and meta-analysis published in 2015, however, did find evidence suggesting that cannabinoids were associated with weight gain in patients with HIV.⁵ Dronabinol has had FDA approval for treatment of weight loss associated with AIDS-related anorexia since 1992.

Before you recommend medical marijuana...

Although medical marijuana is not actually “prescribed,” there are steps to take before recommending or facilitating its use for a particular patient (TABLE 2).²⁵⁻²⁹

After ensuring that he or she has a condition for which there is evidence to support it, you need to do a risk evaluation, drawing on the opioid-prescribing paradigm to look for contraindications to the use of a controlled substance or factors that indicate the need for additional precaution (TABLE 3).^{10,25,26}

Take a thorough medical history and use screening tools

A thorough patient and family medical history, along with principles of Screening, Brief Intervention, and Referral for Treatment (SBIRT), can be used to identify addiction-prone substance use.²⁸ You can also use a validated tool such as the Cannabis Use Disorder Test (CUDIT-R), available at <http://sfmi.wufoo.com/forms/qulgngl12rydww/>. Body fluid (usually urine) testing is also recommended.³⁰ You may be able to access your state’s Prescription Drug Monitoring Program to check for worrisome prescribing, as well.

Stratify risk

The next step is to determine whether the patient is at low, intermediate, or high risk for use of a controlled substance based on your findings. Patients who are younger than 25 years, for example, have an increased risk. And high-risk patients—those with a history of substance abuse, psychiatric illness, or sexual trauma—are unlikely to be good candidates for medical marijuana^{10,25,26} and should be informed in a nonjudgmental manner that their problem is better addressed without it.

If the risk/benefit balance is favorable and the patient is willing to give medical marijuana a try, complete a signed certification of a medical condition for which medical marijuana is authorized in your state. Details of state laws are available at medicalmarijuana.procon.org/view.resource.php?resourceID=000881.

Because the individuals who dispense medical marijuana have varying skills, physicians should collaborate with clinicians judged to be knowledgeable about the best strains of marijuana, the best administration route, and the lowest effective dose—typically a pain management specialist or a physician experienced in recommending medical marijuana appropriately.

Vaporization of marijuana, for use with an inhalation device, may prevent some of the potentially negative consequences of smoking it.³¹ Vaporizing is thought to eliminate some of the irritating—and possibly carcinogenic—materials contained in marijuana smoke.

TABLE 2
Before you recommend medical marijuana: A guide²⁵⁻²⁹

| |
|--|
| Before treatment: |
| <ul style="list-style-type: none"> Determine the diagnosis and need for treatment |
| <ul style="list-style-type: none"> Ensure that other options, including FDA-approved cannabinoids and non-drug approaches, have been tried and proven inadequate |
| <ul style="list-style-type: none"> Conduct a risk evaluation, including contraindications, precautions, and potential adverse effects; use risk stratification to identify the patient as low, intermediate, or high risk |
| <ul style="list-style-type: none"> Consult with a knowledgeable clinician on product selection, dosage, and administration route |
| <ul style="list-style-type: none"> Obtain informed consent, execute a controlled substance agreement, and review proper storage |
| <ul style="list-style-type: none"> Prepare certification indicating that the patient has a medical condition for which your state authorizes the use of medical marijuana |
| During treatment: |
| <ul style="list-style-type: none"> Schedule regular visits to assess symptom and functional efficacy, conduct urine/drug testing, and monitor adherence |
| <ul style="list-style-type: none"> Adjust or discontinue the treatment plan, if necessary, to manage any aberrant behavior that may arise |

Follow risk mitigation principles

Because marijuana is a controlled substance, you will need to talk to the patient about how to store and, if necessary, dispose of it to avoid the risk of diversion—a major concern about the legalization of marijuana.

You can cite a small study of adolescents in substance abuse treatment, in which 3 out of 4 reported having used someone else’s medical marijuana a median of 50 times.³² Adolescents who used medical marijuana had an earlier age of regular marijuana use, more marijuana abuse, and more dependence and conduct disorder symptoms compared with teens who had not used medical marijuana.³²

It is important, too, to obtain informed consent and draw up a controlled substance

> Diversion of medical marijuana is a major concern; patients should be advised to store it safely.

TABLE 3

Should you think twice?
Red flags to consider^{10,25,26}

| Contraindication/precaution | SOR |
|--|-----|
| High risk for cannabis use disorder | B |
| Any active addiction | C |
| Age <25 years old* | B |
| Pregnant or planning to become pregnant | B |
| Safety-sensitive job | B |
| Significant respiratory, cardiac, or vascular disease | B |
| Significant dyscognition, depression, or anxiety | C |
| High risk for psychosis | A |
| Concurrent use of opioids, benzodiazepines, or alcohol | C |
| Tobacco smoking | C |

SOR, strength of recommendation.

*With possible exception for cannabidiol.

agreement, signed by the patient and you. The agreement should outline expected patient behavior, including regular monitoring and body fluid testing, and the consequences of a lack of adherence. (Using a certified laboratory for drug testing is important, as it avoids the possibility of actions based on inaccurate in-office screening.³³) Regular follow-up also provides an opportunity to assess symptom and functional improvement.

If the patient fails to keep appointments and does not respond to efforts to address the problem, the marijuana recommendation may have to be rescinded. Adverse effects, continued aberrant behavior, or evidence of

cannabis use disorder may necessitate immediate cessation of the drug. Depending on the scope of the problem, collaboration with addiction therapy may be necessary. Discharge from the practice, of course, should be the last resort.

CASE ► At a subsequent visit—after a trial with the maximal dose of dronabinol—Ms. B states that although she had some relief, she continues to have a high degree of breakthrough pain. You suspect that medical marijuana may do more to alleviate her pain, and establish a regimen to quickly taper her off dronabinol.

You consult with a pain management specialist, who suggests that the patient begin with raw marijuana with a 10% THC content, smoking 0.6 gm tid. You obtain informed consent and ask her to sign a controlled substance agreement, explaining that you will need to monitor her closely for dizziness, dysphoria, and hallucinations, among other adverse effects. You instruct her not to drive for 6 hours after smoking marijuana, and you schedule a follow-up appointment in 2 weeks.

Before she leaves, Ms. B receives a copy of your clinic note and written recommendation that she can take to the state dispensary. The note indicates that she will use marijuana for neuropathic pain. **JFP**

CORRESPONDENCE

Julius Metts, MD, California Substance Abuse Treatment Facility and State Prison, CDCR, 900 Quebec Avenue, Corcoran, CA 93212; julius.metts@cdcr.ca.gov.

References

- Office of National Drug Control Policy. Marijuana Resource Center. State Laws Related to Marijuana. Available at: <https://www.whitehouse.gov/ondcp/state-laws-related-to-marijuana>. Accessed December 12, 2015.
- American Academy of Family Physicians. AAFP policies: marijuana. Available at: <http://www.aafp.org/about/policies/all/marijuana.html>. Accessed January 16, 2016.
- American College of Physicians. Supporting research into the therapeutic role of marijuana. Available at: https://www.acponline.org/acp_policy/policies/supporting_medmarijuana_2008.pdf. Accessed January 26, 2016.
- Institute of Medicine. Marijuana and medicine: assessing the science base. Available at: <http://iom.nationalacademies.org/reports/1999/marijuana-and-medicine-assessing-the-science-base.aspx>. Accessed January 26, 2016.
- Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313:2456-2473.
- Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *JAMA*. 2015;313:2474-2483.
- Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomized placebo controlled trial. *Lancet*. 2003;362:1517-1526.
- Zajicek JP, Hobart JC, Slade A, et al. MUSEC research group. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry*. 2012;83:1125-1132.
- Koppel BS, Brust JCM, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82:1556-1563.
- Kahan M, Srivastava A, Spithoff S, et al. Smoked CB for chronic noncancer pain. *Can Fam Physician*. 2014;60:1083-1090.
- Todaro B. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. *J Natl Compr Canc Network*. 2012;10:487-492.
- Tramer MR, Carroll D, Campbell FA, et al. Cannabinoids for con-

trol of chemotherapy induced nausea and vomiting: quantitative systemic review. *BMJ*. 2001;323:16-21.

13. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol*. 2002;20:567-573.
14. Hu SS, Mackie K. Distribution of the endocannabinoid system in the central nervous system. *Handbook Exp Pharmacol*. 2015;35:764-774.
15. Bhattacharyya S, Morrison PD, Fusar-Poli P. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*. 2010;35:764-774.
16. Hazekamp A, Ware MA, Muller-Vahl KR, et al. The medicinal use of cannabis and cannabinoids - an international cross sectional survey on administration forms. *J Psychoactive Drugs*. 2013;45:199-210.
17. ProCon.org site. 10 pharmaceutical drugs based on cannabis. Available at: <http://medicalmarijuana.procon.org/view-resource.php?resourceID=000883>. Accessed January 28, 2016.
18. Cerda M, Wall M, Keyes KM, et al. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana, abuse and dependence. *Drug Alcohol Depend*. 2012;120:22-27.
19. US Food and Drug Administration. Inter-agency advisory regarding claims that smoked marijuana is a medicine. April 20, 2006. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108643>. Accessed January 29, 2016.
20. Marinol dronabinol capsules. Available at: www.marinol.com. Accessed January 29, 2016.
21. Cesamet full prescribing information. Available at: <http://www.cesamet.com/patient-home.asp>. Accessed January 29, 2016.
22. Aoyagi T, Terracini KP, Raza A, et al. Cancer cachexia, mechanism and treatment. *World J Gastrointest Oncol*. 2015;7:17-29.
23. Strasser F, Lafner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9 tetrahydrocannabinol (THC) in treating patients with cancer-related anorexia cachexia syndrome, a multicenter, randomized, double blind controlled clinical trial from the Cannabis-In Cachexia Study Group. *Clin Oncol*. 2006;24:3394-3400.
24. Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database Syst Rev*. 2013;(4):CD005175.
25. Phillips JA, Holland MG, Baldwin DD. Marijuana in the workplace: guidance for occupational health professionals and employers: Joint Guidance Statement of the American Association of Occupational Health Nurses and the American College of Occupational and Environmental Medicine. *J Occup Environ Med*. 2015;57:459-475.
26. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Phys*. 2012;15:ES67-ES92.
27. Lopez-Quintero C, de los Cabos JB, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2011;115:120-130.
28. Strobbe S. Prevention and screening, brief intervention and referral to treatment for substance use in primary care. *Primary Care*. 2014;41:185-213.
29. Ehlers CL, Gizer IR, Vieten C, et al. Cannabis dependence in the San Francisco Family Study: age of onset of use, DSM-IV symptoms, withdrawal, and heritability. *Addict Behav*. 2010;35:102-110.
30. American Society of Addiction Medicine. Drug testing: a white paper of the American Society of Addiction Medicine. Available at: <http://www.asam.org/docs/default-source/public-policy-statements/drug-testing-a-white-paper-by-asam.pdf?sfvrsn=2>. October 26, 2013. Accessed January 26, 2016.
31. Tomar RS, Beaumont J, Hsieh JCY. Evidence on the carcinogenicity of marijuana smoke. California EPA: Reproductive and Cancer Hazard Assessment Branch of the Office of Environmental Health Hazard Assessment. August 2009. Available at: http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/FinalMjsmokeHID.pdf. Accessed January 29, 2016.
32. Salomonsen-Sautel S, Sakai JT, Thurstone C. Medical marijuana use among adolescents in substance abuse treatment. *J Am Acad Child Adolesc Psychiatry*. 2012;7:694-702.
33. Reisfield GM, Goldberger BA, Bertholf RL. 'False-positive' and 'false-negative' test results in clinical urine drug testing. *Bioanalysis*. 2009;1:937-952.

NOW ONLINE AT JFPPONLINE.COM

A supplement to the Journal of Family Practice

Hot Topics in Primary Care

Discussion of primary care topics includes:

- Ambulatory Glucose Profiling
- Antihyperglycemic Therapy
- Asthma and Allergic Rhinitis
- Colorectal Cancer Screening
- Opioid-induced Constipation
- Familial Hypercholesterolemia
- Management of Gout
- Innovations in Insulin
- Irritable Bowel Syndrome
- Kidney in Diabetes
- Nonsteroidal Anti-inflammatory Drugs
- Obesity Management



This supplement is sponsored by Primary Care Education Consortium.