Cannabis in Palliative Medicine: Improving Care and Reducing Opioid-Related Morbidity

Gregory T. Carter, Aaron M. Flanagan, Mitchell Earleywine, Donald I. Abrams, Sunil K. Aggarwal and Lester Grinspoon

AM J HOSP PALLIAT CARE 2011 28: 297 originally published online 28 March 2011
DOI: 10.1177/1049909111402318

American Journal of Hospice
& Palliative Medicine®
28(5) 297-303

DOI: 10.1177/1049909111402318
http://ajhpm.sagepub.com

Cannabis in Palliative Medicine: Improving Care and Reducing Opioid-Related Morbidity

Gregory T. Carter, MD, MS[1], Aaron M. Flanagan, MD[2], Mitchell Earleywine, PhD[3], Donald I. Abrams, MD[4], Sunil K. Aggarwal, MD, PhD[5], and Lester Grinspoon, MD[6,7]

Abstract

Unlike hospice, long-term drug safety is an important issue in palliative medicine. Opioids may produce significant morbidity. Cannabis is a safer alternative with broad applicability for palliative care. Yet the Drug Enforcement Agency (DEA) classifies cannabis as Schedule I (dangerous, without medical uses). Dronabinol, a Schedule III prescription drug, is 100% tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis. Cannabis contains 20% THC or less but has other therapeutic cannabinoids, all working together to produce therapeutic effects. As palliative medicine grows, so does the need to reclassify cannabis. This article provides an evidence-based overview and comparison of cannabis and opioids. Using this foundation, an argument is made for reclassifying cannabis in the context of improving palliative care and reducing opioid-related morbidity.

Keywords

cannabis, medical marijuana, opioids, hospice, chronic pain, palliative medicine

Introduction

Palliative care medicine is a relatively new subspecialty, arising out of a need for better ways to treat patients with advanced, potentially "life-limiting" conditions. As palliative medicine emergences as a sovereign entity, distinctly different from hospice care, more practitioners are broadening the scopes of their practice to include these services. However, this will require a distinct paradigm shift, away from the "hospice mindset" with respect to the way drugs are prescribed, with drug safety becoming an increasingly important issue. When treating pain in a terminal cancer patient, using opioid drugs will typically provide good relief.[1] However, in hospice, mortality is a forthcoming and expected outcome. This may not be the case in palliative medicine where the patients seek aggressive treatment for pain yet death may not occur for some time. Here, the successful use of opioids will warrant more frequent patient reassessments and significant pharmacovigilance.

This growth in palliative medicine comes at a time when there have been near epidemic increases in deaths related to prescription of opioid analgesics.[2-13] A number of studies have now clearly linked risk of fatal and nonfatal opioid overdose to prescription use, with the risk increasing with the prescribed dosages.[12-14] According to the Centers for Disease Control and Prevention (CDC), from the years 1999 to 2006, the number of prescription opioid poisoning deaths in the United States (US) nearly doubled, from approximately 20 000 to 37 000.[15] This increase coincided with a nearly 4-fold increase in the use of prescription opioids nationally.

In 2006, Washington State had a rate of poisoning involving opioid painkillers significantly higher than the national rate.[15] A subsequent analysis of overdose deaths involving prescription opioids from 2004 to 2007 revealed that 1668 persons died from prescription of opioid-related overdoses during that time period.[15] Nearly 60% of decedents were male, with most deaths occurring in the 45 to 54 years of age range.[15] A 7-fold higher death rate was noted among persons enrolled in Medicaid programs, compared to those not enrolled. The opioids most commonly involved in the deaths were methadone (64%),

[1] Hospice Services, Providence Medical Group, Olympia, WA, USA
[2] Providence Medical Group, Olympia, WA, USA
[3] Department of Psychology, University at Albany State University of New York, Albany, NY, USA
[4] University of California, San Francisco, CA, USA
[5] Physical Medicine and Rehabilitation, The Rusk Institute of Rehabilitation Medicine, New York University, USA
[6] Department of Psychiatry, Harvard Medical School, USA
[7] Massachusetts Mental Health Center, Boston, MA, USA

Corresponding Author:
Gregory T. Carter, 410 Providence Lane, Building 2, Olympia, WA 98531, USA
Email: gtcarter@uw.edu

oxycodone (23%), and hydrocodone (14%), which highlights the particular toxicity of methadone.[15]

Contrast these morbid trends with this well-documented fact: no one has ever died from an overdose of cannabis.[16-20] Cannabis has no known lethal dose.[16-20] If cannabis-based medicines were more widely used to treat pain, potentially thousands of deaths from opioid toxicity may have been prevented. In the past decade, many states have relegalized cannabis for medicinal purposes.[21] This is based on a continually growing body of evidence demonstrating the efficacy of cannabis in treating neuropathic pain, muscle spasms, fibromyalgia, cacechexia, among others conditions.[21-36] Yet, the laws differ considerably from state to state, with considerable ambiguity what constitutes acceptable medical use.[23] Despite state laws, the Federal United States Drug Enforcement Agency (DEA) laws, as determined by the Controlled Substances Act (CSA), still classify cannabis as a Schedule I drug, the most tightly restricted category, reserved for drugs that have no currently accepted medical use. Thus, there is uniform set of quality control standards in place to assure the quality, consistency, and availability of medicinal cannabis for patients receiving palliative care.

How Did We Get Here?

Against the advice of the American Medical Association, the use of cannabis for any purpose, including medicinal, was criminalized in the United States by 1942.[37-40] Prior to then, there were many cannabis-based medications commercially manufactured by companies including Eli-Lilly, Parke Davis, and Sharp Dohme (now Merck Sharp Dohme).[1] Cannabis was criminalized largely due to the actions of Harry Anslinger, head of the Federal Bureau of Narcotics in the 1930s, who was a notoriously strong opponent of cannabis.[38] Multiple government-sponsored panels, including the National Commission on Marijuana and Drug Abuse (the Shafer Commission), appointed by the then President Richard Nixon have recommended that possession of cannabis for personal use no longer be an offense and that casual distribution of small amounts of cannabis for no remuneration or insignificant remuneration no longer be an offense.[40] The commission further concluded that neither the cannabis user nor the drug itself can be said to constitute a danger to public safety.[40] Despite the commission's recommendations, an infuriated Nixon and Congress ignored the report. Since then, almost 15 million Americans have been arrested on cannabis charges, with little evidence of any impact on cannabis use in either adults or youths.[41-53]

Thus, over the past 75 years, there have been further developments in opioid-based medicine, while research in cannabinoid-based medicines has grounded nearly to a halt. Today, opioids are available in a multitude of strengths, in pills, patches, injectables, implantables, etc, while the only form of a cannabinoid-based medicine available in the United States is dronabinol (Marinol). Dronabinol is 100% Delta-9 tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis.[54] Natural cannabis contains, at most, 20% THC.[55-57]

Opioids versus Cannabinoids: A Brief Overview

Opioids and cannabinoids have many things in common. They are both among the world's oldest-known class of drugs, with documentation of usage dating back many thousands of years. They both produce their pharmacological effect via actions at specific receptors, found throughout the body.[1,21] Both of these classes of compounds are also made endogenously in the human body and are part of the normal regulatory, homeostatic processes necessary for life.[58-61] Without endorphins (opioids) and endocannabinoids (cannabinoids), our bodies would not function properly.

Opioids

Any chemical that works by binding to opioid receptors is considered an opioid.[62,63] Opioid receptors are found principally in the central and peripheral nervous system and the gastrointestinal tract.[63] The receptors in these organ systems mediate both the beneficial and untoward side effects of opioids.[63,64]

In hospice and palliative care, opioids are the "gold standard" for analgesic medications, being cost- and clinically effective, and generally well-tolerated for treating moderate–to-severe pain. However, in a recent study of 50 641 persons receiving hospice services, approximately 20% had moderate or severe constipation due to morphine use.[65] However, long-term toxicity is not an issue in hospice but becomes a major problem in the management of chronic pain.

Cannabinoids

There are 2 known cannabinoid receptor subtypes. Subtype 1 (CB1) is expressed primarily in the brain, whereas subtype 2 (CB2) is expressed primarily in the periphery.[61,66-70] Dense CB1 receptor concentrations have been found in the cerebellum, basal ganglia, and hippocampus, accounting for the effects of cannabis on motor tone, coordination, and mood state.[71-81] Low concentrations are found in the respiratory centers of the brainstem, accounting for the remarkably low toxicity of cannabis.[81] Lethal doses for cannabis in humans have not been described.[1]

A detailed biochemical discussion of the remarkably complex cannabis genus is beyond the scope of this article. There are at least 3 species: cannabis sativa, cannabis indica, and cannabis ruderalis, with each containing over 400 distinct chemical moieties.[82-85] There are at least 85 known cannabinoids that have been isolated from the cannabis plant.[82-85] The cannabinoids are lipophilic, 21 carbon terpenes, and include delta-9 THC and delta-8 THC, which produce the majority of psychoactive effects.[54] Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which significantly modify the effects THC and have distinct effects of their own. CBD appears to modulate and reduce any untoward effects of THC.[83-90] Much less is known about CBN, although it appears to have distinct pharmacological properties that are quite different from CBD.[83] Cannabadiol has significant

anticonvulsant, sedative, and other pharmacological activities likely to interact with the effects of THC.[83] Cannabadiol may induce sleep and may provide some protection against seizures for epileptics.[83] Of relevance for pain management, in addition to analgesia, the following dose-dependent pharmacologic actions have been observed in studies: muscle relaxation, anti-inflammatory effects, neuroprotection in ischemia and hypoxia, enhanced well-being, and anxiolysis.[1-4] The ratios of the various cannabinoids differ according to the plant strain, and, to some extent, how the plant is grown.[82]

Potential analgesic sites of action for cannabinoids have been identified at brain, spinal cord, and peripheral levels.[87-90] There are strong data indicating that neurons in the rostroventral medulla and periaqueductal grey are involved in the brain-mediated analgesic effects of cannabinoids.[91] There are also spinal mechanisms of analgesia, including cannabinergic inhibition of gamma amino butyric acid (GABA), glycine, and glutamate release.[66,71,72] There is also a growing body of evidence showing a peripheral analgesic action of cannabinoids, particularly if inflammation is present.[76] Animal studies have demonstrated analgesic effects of locally delivered cannabinoids at doses that would not be systemically effective.[60] The mechanisms of these peripheral analgesic actions are not completely understood, but appear to be related to the anti-inflammatory effects of cannabinoids.[59,61] Cannabinoids have profound effects on cytokine production, although the direction of such effects is variable and not always mediated by cannabinoid receptors.[81] Another proposed mechanism for the anti-inflammatory actions is cannabinoid-induced increased production of eicosanoids that promote the resolution of inflammation. This differentiates cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process.[92,93]

The Argument Against Dronabinol

Dronabinol is 100% delta-9 THC, the most psychoactive ingredient in cannabis.[54] Natural cannabis contain, at best, 20% THC.[55,56] There are varying physiological effects when the other cannabinoid forms are present, as is the case with natural cannabis plant material.[94] The Food and Drug Administration first licensed and approved dronabinol in 1986 for the treatment of nausea and vomiting associated with chemotherapy and expanded this in 1992 for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS) wasting.[94] Most patients find dronabinol too sedating and associated with too many psychoactive effects.[2,14] Dronabinol is not an appropriate substitute for natural cannabis.

Re-scheduling Cannabis

As previously noted, drugs are categorized (scheduled) by the DEA, as determined by the CSA. Schedule I is a category of drugs not considered legitimate for medical use because of limited utility and a high potential for dependence. Sharing this schedule with cannabis are heroin, lysergic acid, and methamphetamine. Schedule II is a category of drugs considered to have a strong potential for abuse or addiction, but that also have legitimate medical use. Included here are opium, morphine, cocaine, and oxycodone. Schedule III drugs are felt to have even less abuse or addiction potential than Schedule I or II drugs and have a beneficial medical use. Included here are dronabinol, hydrocodone, amphetamine-based stimulants, and short-acting barbiturates. Schedule IV and V drugs are felt to have even less risks. Schedule IV drugs include benzodiazepines, while Schedule V drugs include antidiarrheals and antitussives that contain opioid derivatives.

For further perspective, while the DEA considers cannabis a Schedule I drug, it does not schedule carisoprodol (Soma) at all, implying that this agency does not consider it a dangerous drug. Carisoprodol is a widely used muscle relaxant whose active metabolite is the barbiturate meprobamate. Carisoprodol also shows serotonergic activity at higher levels and has produced overdose in humans.[95,96] Abrupt cessation in patients taking large doses of carisoprodol will produce withdrawal, characterized by vomiting, insomnia, tremors, psychosis, and ataxia.[95,96]

Given that dronabinol, being 100% THC and highly psychoactive, is Schedule III, and the potentially addictive drug carisoprodol is unscheduled, it is perplexing how cannabis remains a Schedule I drug. In our opinion, ideally cannabis should be unscheduled. At the very least, it should be reclassified to Schedule III or higher.

Debunking the Smoking Argument

Cannabis does not need to be smoked to be effectively used as medicine. While cannabis smoke does not cause lung cancer, it can potentially irritate bronchial mucosal membranes. However, cannabinoids are volatile and will vaporize at temperatures in the range of 250°F, much lower than actual combustion.[97-99] Heated air is drawn through cannabis and the active compounds vaporize, which are then inhaled. This rapid deliver of the cannabinoids allows for easy titration to desired effect, much as with smoking yet without health risks.[97-99] Additionally, cannabis can be ingested orally or applied topically in a liniment.[1]

Side Effects of Cannabis

As with any drug, cannabis is not without side effects. Medical use of cannabis is also distinctly different from recreational use. A patient does not need to be intoxicated to get a beneficial medical effect.[100,101] Cannabis may induce euphoria and, as such, may be psychologically addictive. There is no severe physical withdrawal syndrome associated with cannabis. Cannabis addiction is amenable to treatment.[46] Cannabis may induce paranoia and disorientation in novice users. Many of the undesired psychoactive effects of cannabis are due to THC, which is among the reasons that dronabinol is not a suitable alternative.

However, newer medicinal strains of cannabis are lower in THC and higher in the nonpsychoactive, more therapeutic cannabinoids, such as CBD and CBN. These compounds further improved the efficacy of cannabis.[102-104] With simple trial and error, most patients are able to get the right combination of cannabinoids that meet their needs. Dosing paradigms for medicinal cannabis have been previously described.[17,18]

Conclusion

Despite being hampered by legal restrictions, the available medical research on cannabis indicates that cannabis is effective in treating a number of problems commonly encountered in palliative medicine. Many patients in a palliative care setting who are currently on long-term opioids for chronic pain could potentially be treated with either cannabis alone or in combination with a lower dose of opioids. From a pharmacological perspective, cannabinoids are considerably safer than opioids and have broad applicability in palliative care. Had cannabis not been removed from our pharmacopeia 7 decades ago and remained available to treat chronic pain, potentially thousands of lives that have been lost to opioid toxicity could have been prevented. As our population ages and palliative medicine continues to grow as a specialty, the argument for cannabis to be reclassified by the DEA as a scheduled III or higher becomes increasingly important.

As palliative medicine practitioners, our specialty should embrace the scientific process, which continues to document the therapeutic effects of cannabis. As is often the case in hospice, we must be willing to advocate for our patients who want to legitimately access a medicine that could potentially be very beneficial for them and is safer than other options such as opioids. The medicinal cannabis user should not be considered a criminal in any state and the DEA and our legal system should be using science and logic as the basis of policy making rather than political or societal bias.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References

1. Vigano A, Bruera E, Suarez-Almazor ME. Age, pain intensity and opioid dose in patients with advanced cancer. *Cancer*. 1998; 83(6):1244-1250.
2. Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L. Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. *Am J Ind Med*. 2005;48(2): 91-99.
3. Jumbelic MI. Deaths with transdermal fentanyl patches. *Am J Forensic Med Pathol*. 2010;31(1):18-21.
4. Campbell CI, Weisner C, Leresche L, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. *Am J Public Health*. 2010;100(12):2541-2547.
5. Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med*. 2010;170(22):1979-1986.
6. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: a prospective, population-based study among injured workers in Washington state, 2002-2005. *Clin J Pain*. 2009;25(9):743-751.
7. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010;170(22):1968-1978.
8. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008;8(4):287-313.
9. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *BMJ*. 2010;26(341):c5475.
10. Wunsch MJ, Nakamoto K, Nuzzo PA, Behonick G, Massello W, Walsh SL. Prescription drug fatalities among women in rural Virginia: a study of medical examiner cases. *J Opioid Manag*. 2009; 5(4):228-236.
11. Paulozzi LJ, Xi Y. Recent changes in drug poisoning mortality in the United States by urban-rural status and by drug type. *Pharmacoepidemiol Drug Saf*. 2008;17(10):997-1005.
12. Shah NG, Lathrop SL, Reichard RR, Landen MG. Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction*. 2008;103(1):126-136.
13. Coffin PO, Galea S, Ahern J, Leon AC, Vlahov D, Tardiff K. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in New York City, 1990-98. *Addiction*. 2003; 98(6):739-747.
14. Piercefield E, Archer P, Kemp P, Mallonee S. Increase in unintentional medication overdose deaths: Oklahoma, 1994-2006. *Am J Prev Med*. 2010;39(4):357-363.
15. Centers for Disease Control and Prevention (CDC). Overdose deaths involving prescription opioids among Medicaid enrollees - Washington, 2004-2007. *MMWR Morb Mortal Wkly Rep*. 2009;58(42):1171-1175.
16. Walden N, Earleywine M. How high: quantity as a predictor of cannabis-related problems. *Harm Reduct J*. 2008;5:20.
17. Aggarwal SK, Kyashna-Tocha M, Carter GT. Dosing medical marijuana: rational guidelines on trial in Washington State. *Med Gen Med*. 2007;9(3):52.
18. Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. Medical marijuana: rational guidelines for dosing. *IDrugs*. 2004;7(5): 464-470.
19. Klein TW, Lane B, Newton CA, Friedman H. The cannabinoid system and cytokine network. *Proc Soc Exp Biol Med*. 2000; 225(1):1-8.

20. Pertwee RG. Cannabinoid receptor ligands: clinical and neuropharmacological considerations, relevant to future drug discovery and development. *Expert Opin Investig Drugs*. 2000;9(7): 1553-1571.
21. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions. *J Opioid Manag*. 2009;5(3):153-168.
22. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Characteristics of patients with chronic pain accessing treatment with medicinal cannabis in Washington State. *J Opioid Manag*. 2009;5(5):257-286.
23. Carter GT, Mirken B. Medical marijuana: politics trumps science at the FDA. *Medscape Gen Med*. 2006;8(2):46.
24. Carter GT, Rosen BS. Marijuana in the management of amyotrophic lateral sclerosis. *Am J Hosp Palliat Care*. 2001;18(4): 264-270. PMID:11467101.
25. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010; 182(14):E694-E701.
26. El-Alfy AT, Ivey K, Robinson K, et al. Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from *Cannabis sativa L*. *Pharmacol Biochem Behav*. 2010; 95(4):434-442.
27. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2008;(2):1-9.
28. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9:506-521.
29. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68(7):515-521.
30. Abrams DI, Vizoso HP, Shade SB, et al. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther*. 2007;82(5):572-578.
31. Rocha FCM, Oliveira LMQR, Da Silveira DX. Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care*. 2008;17(4):431-443.
32. Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J. Neuroprotective antioxidants from marijuana. *Ann N Y Acad Sci*. 2000;899:274 82.
33. Nagayama T, Sinor AD, Simon RP, et al. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. *J Neurosci*. 1999;19(8):2987 95.
34. Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT. Survey of cannabis use in patients with amyotrophic lateral sclerosis. *Am J Hosp Palliat Care*. 2004;21(2):95-104.
35. Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoactive Drugs*. 1998;30(2):171-177.
36. Denson TF, Earleywine M. Decreased depression in marijuana users. *Addict Behav*. 2006;31(4):738-42.
37. Carter GT, Abood ME, Aggarwal SK, Weiss MD. Cannabis and amyotrophic lateral sclerosis: practical and hypothetical applications, and a call for clinical trials. *Am J Hosp Palliat Med*. 2010;27(5):347-356.
38. McWilliams JC. Unsung partner against crime: Harry J. Anslinger and the Federal Bureau of Narcotics, 1930-1962. *Pa Mag Hist Biogr*. 1989;113(2):207-236.
39. Hollister LE. Criminal laws and the control of drugs of abuse. An historical view of the law (or, it's the lawyer's fault). *J Clin Pharmacol J New Drugs*. 1969;9(6):345-348.
40. Nahas GG, Greenwood A. The first report of the National Commission on marihuana (1972): signal of misunderstanding or exercise in ambiguity. *Bull N Y Acad Med*. 1974;50(1):55-75.
41. Paschall MJ, Flewellng RL, Grube JW. Using statewide youth surveys to evaluate local drug use policies and interventions. *Contemp Drug Probl*. 2009;36(3-4):427-446.
42. Eaton DK, Kann L, Kinchen S, et al. Centers for Disease Control and Prevention (CDC): Youth risk behavior surveillance – United States, 2009. *MMWR Surveill Summ*. 2010;59(5):1-142.
43. Grinspoon L, Bakalar JB, Zimmer L, Morgan JP. Marijuana addiction. *Science*. 1997;277(5327):749.
44. Barnwell SS, Earleywine M. Simultaneous alcohol and cannabis expectancies predict simultaneous use. *Subst Abuse Treat Prev Policy*. 2006;1(11):29.
45. Earleywine M. Schizotypy, marijuana, and differential item functioning. *Hum Psychopharmacol*. 2006;21(7):455-461.
46. Denson TF, Earleywine M. Pothead or pot smoker? A taxometric investigation of cannabis dependence. *Subst Abuse Treat Prev Policy*. 2006;10(1):22.
47. Barnwell SS, Earleywine M, Wilcox R. Cannabis, motivation, and life satisfaction in an internet sample. *Subst Abuse Treat Prev Policy*. 2006;12(1):2.
48. Smucker Barnwell S, Earleywine M, Gordis EB. Alcohol consumption moderates the link between cannabis use and cannabis dependence in an internet survey. *Psychol Addict Behav*. 2005; 19(2):212-216.
49. Earleywine M. Marijuana arrests and increase in marijuana use disorders. *JAMA*. 2004;292(7):802.
50. Grinspoon L, Bakalar JB. The war on drugs–a peace proposal. *N Engl J Med*. 1994;330(5):357-60.
51. Looby A, Earleywine M. Negative consequences associated with dependence in daily cannabis users. *Subst Abuse Treat Prev Policy*. 2007;10(2):3.
52. Lavender JM, Looby A, Earleywine M. A brief cannabis-associated problems questionnaire with less potential for bias. *Hum Psychopharmacol*. 2008;23(6):487-493.
53. Van Dam NT, Earleywine M, DiGiacomo G. Polydrug use, cannabis, and psychosis-like symptoms. *Hum Psychopharmacol*. 2008;23(6):475-485.
54. Taylor EC, Lenard K, Loev B. Tetrahydrocannabinol analogs. Synthesis of 2-(3-methyl-2-octyl)-3-hydroxy-6,6,9-trimethyl-7,8, 9,10-tetrahydrodibenzo(b,d)pyran. *Tetrahedron*. 1967;23(1):77-85.
55. Etienne PM, de Meijer M, Bagatta A, et al. The inheritance of chemical phenotype of *Cannabis sativa L*. *Genetics*. 2003; 163(1):335-346.
56. Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). *Am J Bot*. 2004; 91(6):966-975.

57. Cristiana Moliterni VM, Cattivelli L, Ranalli P, Mandolino G. The sexual differentiation of *Cannabis sativa L*: a morphological and molecular study. *Euphytica*. 2005;140(1-2):95-106.
58. DeSanty KP, Dar MS. Involvement of the cerebellar adenosine A(1) receptor in cannabinoid induced motor incoordination in the acute and tolerant state in mice. *Brain Res*. 2001;29,905(1-2): 178-187.
59. Di Marzo V, Fontana A, Cadas H, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature*. 1994;372(6507):686-691.
60. Egertova M, Elphick MR. Localisation of cannabinoid receptors in the rat brain using antibodies to the intracellular C-terminal of CB1. *J Comp Neurol*. 2000;422:159-171.
61. Tsou K, Brown S, Mackie K, Sanudo-Pena MC, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neuroscience*. 1998;83(2): 393-411.
62. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med.* 2010;18;363(21):1981-1985.
63. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. *J Pain*. 2010;11(9):807-829.
64. Bishop MF, Stephens L, Goodrich M, Byock I. Medication kits for managing symptomatic emergencies in the home: a survey of common hospice practice. *J Palliat Med*. 2009;12(1):37-44.
65. Strassels SA, Maxwell TL, Iyer S. Constipation in persons receiving hospice care. *J Pain. Symptom Manage*. 2010;40(6):810-820.
66. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesic circuit activated by cannabinoids. *Nature*. 1998;395(6700):381-383.
67. Martin WJ, Hohmann AG, Walker JM. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the thalamus by a cannabinoid agonist: Correlation between electrophysiological and antinociceptive effects. *J Neurosci*. 1996; 16(20):6601-6611.
68. Lichtman AH, Cook SA, Martin BR. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: evidence supporting periaqueductal gray involvement. *J Pharmacol Exp Ther*. 1996;276(2):585-593.
69. Tsou K, Brown S, Mackie K, Sanudo-Pena MC, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neuroscience*. 1998;83(2): 393-411.
70. Ong WY, Mackie K. A light and electron microscopic study of the CB1 cannabinoid receptor in the primate spinal cord. *J Neurocytol*. 1999;28(1):39-45.
71. Farquhar-Smith WP, Egertova M, Bradbury EJ, McMahon SB, Rice ASC, Elphick MR. Cannabinoid CB1 receptor expression in rat spinal cord. *Mol Cell Neurosci*. 2000;15:510-521.
72. Hohmann AG, Briley EM, Herkenham M. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Res*. 1999;822(1-2):17-25.
73. Sanudo-Pena MC, Strangman NM, Mackie K, Walker JM, Tsou K. CB1 receptor localization in rat spinal cord and roots, dorsal root ganglion and peripheral nerve. *Acta Pharmacol Sin*. 1999;20(12):1115-1120.
74. Hohmann AG, Herkenham M. Regulation of cannabinoid and mu opioid receptors in rat lumbar spinal cord following neonatal capsaicin treatment. *Neurosci Lett*. 1998;252(1):13-16.
75. Chapman V. The cannabinoid CB1 receptor antagonist, SR141716A, selectively facilitates nociceptive responses of dorsal horn neurones in the rat. *Br J Pharmacol*. 1999;127(8): 1765-1767.
76. Smith PB, Martin BR. Spinal mechanisms of delta 9-tetrahydrocannabinol-induced analgesia. *Brain Res*. 1992; 578(1-2):8-12.
77. Morisset V, Urban L. Cannabinoid-induced inhibition of excitatory transmission in substantia gelatinosa neurones of the rat spinal cord. *Soc Neurosci Abstr*. 2000;26:812-814.
78. Fox A, Kesingland A, Gentry C, et al. The role of central and peripheral CB1 receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. *Pain*. 2001;92(1-2):91-100.
79. Agarwal N, Pacher P, Tegeder I, et al. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. *Nat Neurosci*. 2007;10(7):870-879.
80. Farquhar-Smith WP, Egertova M, Bradbury EJ, McMahon SB, Rice ASC, Elphick MR. Cannabinoid CB1 receptor expression in rat spinal cord. *Mol Cell Neurosci*. 2000;15:510-521.
81. Nguyen PT, Selley DE, Sim-Selley LJ. Statistical Parametric Mapping reveals ligand and region-specific activation of G-proteins by CB1 receptors and non-CB1 sites in the 3D reconstructed mouse brain. *Neuroimage*. 2010;52(4):1243-1251.
82. Fischedick JT, Glas R, Hazekamp A, Verpoorte R. A qualitative and quantitative HPTLC densitometry method for the analysis of cannabinoids in *Cannabis sativa L*. *Phytochem Anal*. 2009;20(5): 421-426.
83. Borrelli F, Aviello G, Romano B, Orlando P, Capasso R, Maiello F, Guadagno F, Petrosino S, Capasso F, Di Marzo V, Izzo AA. Cannabidiol. a safe and non-psychotropic ingredient of the marijuana plant *Cannabis sativa*, is protective in a murine model of colitis. *J Mol Med*. 2009;87(11):1111-1121.
84. Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol*. 2010;159(1): 122-128.
85. Jones NA, Hill AJ, Smith I, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther*. 2010;332(2):569-577.
86. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology*. 2010;35(9):1879-1885.
87. Russo EB. Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuro Endocrinol Lett*. 2008;29(2):192-200.
88. Lakhan SE, Rowland M. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. *BMC Neurol*. 2010;9:59-61.
89. McAllister SD, Hurst DP, Barnett-Norris J, Lynch D, Reggio PH, Abood ME. Structural mimicry in class A G protein-coupled receptor rotamer toggle switches: the importance of the

F3.36(201)/W6.48(357) interaction in cannabinoid CB1 receptor activation. *J Biol Chem*. 2004;279(46):48024-48037.
90. Burstein SH, Zurier RB. Cannabinoids, endocannabinoids, and related analogs in inflammation. *AAPS J*. 2009;11(1):109-119.
91. Lichtman AH, Cook SA, Martin BR. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: evidence supporting periaqueductal gray involvement. *J Pharmacol Exp Ther*. 1996;276(2):585-593.
92. González-Muniesa P, Bing C, Trayhurn P. Upregulation of the expression of inflammatory and angiogenic markers in human adipocytes by a synthetic cannabinoid, JTE-907. *Horm Metab Res*. 2010;42(10):710-717.
93. Cencioni MT, Chiurchiù V, Catanzaro G, et al. Anandamide suppresses proliferation and cytokine release from primary human T-lymphocytes mainly via CB2 receptors. *PLoS One*. 2010;5(1): e8688.
94. Schedules of controlled substances: rescheduling of the Food and Drug Administration approved product containing synthetic dronabinol [(-) - [DELTA] less than 9 greater than - (trans)-tetrahydrocannabinol] in sesame oil and encapsulated in soft gelatin capsules from schedule II to schedule III. Department of Justice (DOJ), Drug Enforcement Administration (DEA). Final rule. *Fed Regist*. 1999;64(127):35928-30.
95. Reeves RR, Burke RS. Carisoprodol: abuse potential and withdrawal syndrome. *Curr Drug Abuse Rev*. 2010;3(1):33-38.
96. Fass JA. Carisoprodol legal status and patterns of abuse. *Ann Pharmacother*. 2010;44(12):1962-7.
97. Van Dam NT, Earleywine M. Pulmonary function in cannabis users: support for a clinical trial of the vaporizer. *Int J Drug Policy*. 2010;21(6):511-513.
98. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. *Harm Reduct J*. 2007;4:11.
99. Melamede R. Cannabis and tobacco smoke are not equally carcinogenic. *Harm Reduct J*. 2005;18(2):21.
100. Grinspoon L, Bakalar JB. Marihuana as medicine. A plea for reconsideration. *JAMA*. 1995;273(23):1875-1876.
101. Grinspoon L, Bakalar JB, Doblin R. Marijuana, the AIDS wasting syndrome, and the U.S. government. *N Engl J Med*. 1995; 333(10):670-671.
102. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain*. 2004;112(3):299-306.
103. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*. 2008;336(7637):199-201.
104. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg*. 2010;110(2):604-610.