

Issue Briefing #4

MEDICAL MARIJUANA

While cannabinoids have demonstrated therapeutic benefit, we stress that this is very limited potential for treating symptoms of very specific conditions and not the diseases themselves. We also have noted that new drugs have recently been developed which have demonstrated clinical efficacy over medical marijuana for certain conditions, and other drugs are on the horizon. We concur with the American Medical Association that **marijuana in smoked form is unsuitable as a medicine**. Additionally, no medication should be utilized without the formal approval of the U.S. Food & Drug Administration, regardless of the action of state legislatures.

Consequently, we recommend: 1) development of a smoke-free inhaled or sublingual delivery system for whole marijuana extract or isolated cannabinoids; in conjunction with, 2) further clinical trials on the efficacy of marijuana and related cannabinoids according to strictly monitored research protocols, per the recommendations of the Institute of Medicine and the American Medical Association.

As discussed in the IOM Report, opium has been processed to yield several therapeutic medications, yet no doctor would advise the smoking of raw opium to a patient. Similarly, marijuana may yield several beneficial medications under strict prescription, but certainly not in raw form.

Introduction

Societal attitudes and policies toward marijuana (*Cannabis sativa*) have varied wildly across eras and cultures, from Draconian penalties for simple possession¹ to veneration as a panacea² and subcultural integration as a recreational drug. Because of this polarization, it may be true that “marijuana is unique among illegal drugs in its political symbolism...”³ Regardless, public health policy decisions are properly based on scientific scrutiny and rigorous policy analysis rather than on ideology,⁴ popular votes,⁵ or folk wisdom⁶. Integral to that scientific process are systematic research reviews,⁷ which tend to limit bias and minimize the methodological flaws found in isolated research studies.⁸ Accordingly, with regard to health evidence, this Issue Briefing considers only systematic research reviews.

Systematic Research Reviews: Medical Marijuana in General

Systematic research reviews on medical marijuana have varied in their findings regarding its value in relieving various symptoms. However, **none** have recommended the long-term therapeutic utilization of marijuana in smoked form (MSF) based on current evidence. To wit:

- ♦ The **American Medical Association** (AMA) recommended further research and “development of a smoke-free inhaled delivery system for marijuana or delta-9-tetrahydrocannabinol (THC) to reduce the health hazards associated with the combustion and inhalation of marijuana.”⁹
- ♦ The **Institute of Medicine** (IOM) similarly determined that MSF should not be “develop[ed] ... as a licensed drug”¹⁰ but instead urged the development of “nonsmoked rapid-onset cannabinoid delivery systems.”¹¹ Unlike the AMA, however, the IOM did recommend some exceptions for compassionate use of MSF under very limited, strictly monitored circumstances.¹²
- ♦ The **U.S. Food and Drug Administration** (FDA) has made clear that it “has not approved smoked marijuana for any condition or disease indication.”¹³

Systematic Research Reviews: Specific Medical Conditions

With regard to specific medical conditions, systematic reviews have found some benefit in cannabinoids, while nearly always finding MSF to be contraindicated:

- ♦ **Analgesia.** The AMA concluded that “controlled evidence does not support the view that THC or smoked marijuana offers clinically effective analgesia without causing significant adverse events when used alone.”¹⁴

- ♦ **Dementia.** The Cochrane Collaboration found “no evidence that cannabinoids are effective in the improvement of disturbed behaviour in dementia or in the treatment of other symptoms of dementia.”¹⁵
- ♦ **Glaucoma.** The Task Force on Complementary Therapies of the American Academy of Ophthalmology determined that “no scientific evidence has been found that demonstrates increased benefits and/or diminished risks of marijuana use to treat glaucoma compared with the wide variety of pharmaceutical agents now available.”¹⁶
- ♦ **HIV-Wasting/AIDS Wasting Syndrome.** Until a smoke-free inhalation system is developed, MSF may have value for this condition. The AMA posits that “the ability of patients who smoke marijuana to titrate their dosage according to need, and the lack of highly effective, inexpensive options to treat this debilitating disease create the conditions warranting a formal clinical trial of smoked marijuana as an appetite stimulant in patients with HIV-wasting syndrome.”¹⁷ The IOM report had expressed reservations regarding immunological effects of MSF,¹⁸ but the AMA noted that “initial safety trials in HIV-positive patients are encouraging regarding a lack of apparent marijuana-induced immunosuppression.”¹⁹ Currently, the Cochrane Collaborative Review Group on HIV Infection and AIDS is addressing the issue of the appetite-stimulating effects of cannabis in the protocol entitled “The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS.” The findings of that review are expected in December of 2009.²⁰
- ♦ **Nausea & Vomiting.** “Cannabinoids are mildly effective in preventing emesis in some patients who are receiving cancer chemotherapy” according to the IOM.²¹ Tramèr and colleagues (2001) found that cannabinoids were generally more effective than conventional antiemetics.²² However, that efficacy was deemed “marginal”²³ and the side effects of cannabinoids (paranoia, hallucinations, dysphoria) were considerable, resulting in the withdrawal from treatment of 1 out of every 11 patients.²⁴
- ♦ **Neurological Disorders: Multiple Sclerosis.** Animal model research and anecdotal evidence suggest that cannabinoids may be beneficial in controlling spasticity, pain, tremor and bladder dysfunction,²⁵ “however, these initially promising results have not yet been fully translated into the clinic” as “...objective measures demonstrating the efficacy of cannabinoids are still lacking.”²⁶ Furthermore, “the regular use of smoked marijuana ... would be contraindicated in a chronic condition like MS.”²⁷

It should be added that there are a number of extant cannabinoid medications – including dronabinol (Marinol®), Sativex®, and nabilone (Cesamet®) – which have shown promise in relieving many of the symptoms described above.²⁸ In view of that, support of the further development of these and related medications is in order.

Systematic Research Reviews: Adverse Effects of MSF

Despite claims by proponents that MSF is harmless,²⁹ its use may have serious consequences.

- ♦ **Neuropsychiatric. Psychosis.** While neither a necessary nor sufficient cause of psychosis, “longitudinal studies suggest that early exposure to cannabis confers a close to two-fold increase in the risk of developing schizophrenia.”³⁰ In addition, marijuana can “exacerbate symptoms, trigger relapse, and worsen the course of the illness” in individuals already diagnosed with psychotic illness.³¹ Several recent reviews have confirmed this link.³²

Dependence and withdrawal. A cannabis dependence syndrome has been identified, affecting about 7-10% of those who use MSF.³³ Moreover, there is a marijuana withdrawal syndrome, which, while “mild and subtle compared with the profound physical syndrome of alcohol or heroin,”³⁴ has symptoms including “restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping.”³⁵

- ♦ **Respiratory.** “Results of human studies suggest that there is a greater chance of respiratory illness in people who smoke marijuana,”³⁶ with a “probable” connection of chronic marijuana smoking to acute and chronic bronchitis and chronic obstructive pulmonary disease (COPD).³⁷
- ♦ **Cardiovascular.** MSF and cannabinoids can cause tachycardia and hypotension, and thus may “present a serious problem for older patients” suffering from, or at risk for, cardiovascular disease.³⁸
- ♦ **Bone.** Cannabis has been shown to negatively affect bone metabolism and bone toxicity.³⁹
- ♦ **Carcinogenic.** The IOM notes that “cellular and molecular studies have provided strong evidence that marijuana smoke is carcinogenic,” while clinical studies have been less conclusive, largely due to methodological challenges.⁴⁰
- ♦ **Other health.** Cannabis smoke is mutagenic (both *in vitro* and *in vivo*).⁴¹ Additionally, MSF also can have teratogenic effects, depending on dose and duration.⁴² Kalant (2004) reports that “a small but growing body of evidence indicates subtle but apparently permanent effects on memory, information processing, and executive functions, in the offspring of women who used cannabis during pregnancy.”⁴³
- ♦ **Violence.** While systematic reviews of the relationship of marijuana to violence have been inconclusively due to the fact that the relationship between substance abuse and violence is “exceedingly complex and moderated by a host of factors in the individual and the environment”, a meta-analysis of 96 studies found that marijuana was identified “having a significant association with partner aggression.”⁴⁴
- ♦ **Service utilization.** According to the Drug Abuse Warning Network (DAWN), in 2006 there were over 290,563 marijuana-related admissions into hospital emergency rooms⁴⁵ (an approximately 278% increase since 1998.)

Additional Considerations

Also necessary to consider with regard to medical marijuana legislation/initiatives is the propensity for fraud and abuse. While it is beyond the scope of this briefing to undertake a full policy analysis of state initiatives to legalize/decriminalize medical marijuana, anecdotal reports suggest that the conditions for use have expanded far beyond their original mandate. In California, in particular, the lax guidelines for use of MSF in Proposition 215 ("for any other illness for which marijuana provides relief"⁴⁶) has resulted in the citing of over 250 separate "medical conditions" for MSF recommendations.⁴⁷ These conditions have ranged from the serious (quadriplegia, Lou Gehrig's disease, pulmonary fibrosis) to the exotic (Henoch-Schönlein purpura, Kashin-Bek disease, eosinophilia myalgia syndrome) to the curious (morbid obesity, writer's cramp, color blindness).⁴⁸

Perhaps not surprisingly, the issue of commercialization has also complicated the situation in California, with marijuana dispensaries becoming "L.A.'s latest retail craze"⁴⁹ and the choice of ambitious "entrepreneurs."⁵⁰ Indeed, some cannabis dispensaries appear to be more like ice-cream parlors or wine boutiques than pharmacies, as they offer a variety of colors and flavors of cannabis in a spa-like atmosphere.⁵¹

In light of this, a reasonable first course of action before any attempt at legalization should include thorough, disinterested evaluation of the other states' initiatives, including possible effects on the incidence of cannabis-related health problems (schizophrenia, COPD, etc.).

Furthermore, it should be noted that pro-legalization groups have made explicit their intention to use the issue of medical marijuana to "reframe" debate in order to effect the complete legalization of recreational marijuana.⁵²

Conclusion

In conclusion, there is nothing magical about medical marijuana that should exempt it from the process required of every other drug. As Peter J. Cohen of the Georgetown University Law Center has stated:

While the FDA's role in drug evaluation is not perfect, deficiencies in its regulation and evaluation of pharmaceuticals should not be taken as an excuse to disregard the fundamental utility of the agency and to abandon the philosophy that science rather than politics should be dispositive with regard to acceptance or rejection of medications.⁵³

Or, to put it another way, we are best served by a policy based on the scientific evidence, rather than having our willingness to take action determine how we process the scientific evidence on marijuana.⁵⁴

Appendix A

Institute of Medicine Recommendation, Compassionate Use for Smoked Marijuana

RECOMMENDATION: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- ♦ failure of all approved medications to provide relief has been documented,
- ♦ the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,
- ♦ such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and
- ♦ involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

Joy, Watson, & Benson, 1999, p. 179

-
- ¹ Cohen, 2009
 - ² Ibid.
 - ³ Annas, 1997, p. 435
 - ⁴ Goldstein, 2001
 - ⁵ Cohen, 2009
 - ⁶ Kington, 2003
 - ⁷ Mulrow, 1994
 - ⁸ Cook, Mulrow, & Haynes, 1997; Mulrow & Lohr, 2001
 - ⁹ American Medical Association [AMA], 2001
 - ¹⁰ Joy, Watson, & Benson, 1999, p. 7
 - ¹¹ Ibid, p. 7
 - ¹² Ibid, p. 179. See Appendix A.
 - ¹³ U.S. Food & Drug Administration (2006)
 - ¹⁴ AMA, 2001
 - ¹⁵ Krishnan, Cairns, & Howard, 2009
 - ¹⁶ Schwab, Chavis, Husted, & Liegner, 2003
 - ¹⁷ AMA, 2001
 - ¹⁸ Joy, Watson, & Benson, 1999, p. 156
 - ¹⁹ AMA, 2001
 - ²⁰ Dr. Elizabeth Lutge (personal communication, September 3, 2009)
 - ²¹ Joy, Watson, & Benson, 1999, p. 148
 - ²² Tramèr, p. 19
 - ²³ Ibid, p. 19
 - ²⁴ Ibid, p. 19
 - ²⁵ Croxford & Miller, 2004
 - ²⁶ Ibid., p. 663
 - ²⁷ Joy, Watson, & Benson, 1999, p. 161
 - ²⁸ Cf. Huestis, 2007
 - ²⁹ Cf. Annas, 1997; O'Connell & Bou-Matar, 2007
 - ³⁰ Sewell, Ranganathan, & D'Souza, 2009, p. 152
 - ³¹ Ibid, p. 152
 - ³² Moore, Zammit, et al., 2007; Ben Amar & Potvin, 2007; Verdoux & Tournier, 2004; although, see also Zammit, Moore, et al., 2008
 - ³³ Kalant, 2004; Hall & Solowij, 1998
 - ³⁴ Joy, Watson, & Benson, 1999, p. 90
 - ³⁵ Ibid, p. 90
 - ³⁶ Ibid, p. 113
 - ³⁷ Ibid, p. 115
 - ³⁸ Ibid, p. 122
 - ³⁹ Reece, 2009
 - ⁴⁰ Joy, Watson, & Benson, 1999, p. 118
 - ⁴¹ Hall & Solowij, 1998, p. 1612
 - ⁴² Reece, 2009
 - ⁴³ Kalant, 2004, p. 849
 - ⁴⁴ Moore, Stuart, et al. 2008
 - ⁴⁵ SAMHSA, 2008
 - ⁴⁶ O'Connell & Bou-Matar, 2004
 - ⁴⁷ Gieringer, 2002
 - ⁴⁸ Ibid.
 - ⁴⁹ Smith & Lauder, 2009
 - ⁵⁰ Ibid.
 - ⁵¹ Seligman, 2007
 - ⁵² Pichardo Almanzar, 2003
 - ⁵³ Cohen, 2009, p. 103
 - ⁵⁴ Marmot, 1994

References:

American Medical Association (2001). *Medical marijuana*. Council on Scientific Affairs Report 6. Retrieved on September 3, 2009, from <http://www.ama-assn.org/ama/no-index/about-ama/13625.shtml>.

Annas, G.J. (1997). Reefer madness — The federal response to California's Medical-Marijuana Law. *New England Journal of Medicine*, 337(6), 435-439.

Arseneault, L., Moffitt, T. E., Caspi, A., et al (2000). Mental disorders and violence in a total birth cohort: Results from the Dunedin study. *Archives of General Psychiatry*, 57(10), 979-986.

Ben Amar, M, & Potvin, S. (2007). Cannabis and psychosis: What is the link? *Journal of Psychoactive Drugs*, 39(2), 131-142.

Boles, S.M., & Miotto, K. (2003). Substance abuse and violence: A review of the literature. *Aggression and Violent Behavior*. 8(2), 155-174.

Cohen, P.J. (2009). Medical marijuana: The conflict between scientific evidence and political ideology. *Utah Law Review*, 2009(1), 35-104.

Cook, D.J., Mulrow, C.D., & Haynes, R.B. (1997). Systematic reviews: Synthesis of best evidence for clinical decisions. *Annals of Internal Medicine*, 126(5), 376-380.

Croxford, J.L. & Miller, S.D. (2004). Towards cannabis and cannabinoid treatment of multiple sclerosis. *Drugs of Today*, 40(8), 663-676.

Gieringer, D. (2002). Medical use of cannabis: Experience in California. In F. Grotenhermen & E. Russo (Eds). *Cannabis and cannabinoids: Pharmacology, toxicology and therapeutic potential* (pp. 143-152). Binghamton, NY: Haworth Press.

Goldstein, A. (2001). *Addiction: From biology to drug policy* (2nd ed). Oxford: Oxford University Press.

Hall, W. & Solowij, N. (1998). Adverse effects of cannabis. *Lancet*, 352(9140), 1611-1616.

Huestis, M.A. (2007). Human cannabinoid pharmacokinetics. *Chemistry & Biodiversity*, 4(8), 1770-1804.

Joy, J.E., Watson, Jr., S.J., & Benson, Jr., J.A., (Eds) (1999). *Marijuana and medicine: Assessing the science base*. Institute of Medicine. Washington, D.C.: National Academies of Science.

Kalant, H. (2004). Adverse effects of cannabis on health: An update of the literature since 1996. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 28(5), 849-863.

Kimhy, D., Durbin, K., & Corcoran, C.M. (2009). Cannabis and psychosis: What can daily diaries tell us about who is vulnerable? *Primary Psychiatry*, 16(4), 44-48.

Kington, R.S. (2003). Point and counterpoint: The critical role of relevance. In *Science meets reality: Recruitment and retention of women in clinical studies, and the critical role of relevance: A report of the Task Force sponsored by the NIH Office of Research on Women's Health* (pp. 26-38). Retrieved on September 10, 2009, from http://orwh.od.nih.gov/pubs/SMR_Final.pdf.

Krishnan, S, Cairns, R, & Howard R. (2009). Cannabinoids for the treatment of dementia. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD007204. DOI: 10.1002/14651858.CD007204.pub2.

Marmot, M.G. (2004). Evidence based policy or policy based evidence? Willingness to take action influences the view of the evidence—look at alcohol [editorial]. *British Medical Journal*, 328(7445), 906-907.

Moore, T.M., Stuart, G.L., Meehan, J.C., Rhatigan, D.L., Hellmuth, J.C., & Keen, S.M. (2008). Drug abuse and aggression between intimate partners: A meta-analytic review. *Clinical Psychology Review*, 28(2), 247-274.

Moore, T.H.M., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., et al. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet*, 370(9584), 319-328.

Mulrow, C.D. (1994). Rationale for systematic reviews. *British Medical Journal*, 309(6954), 597-599

Mulrow, C.D. & Lohr, K.N. (2001). Proof and policy from medical research evidence. *Journal of Health Politics, Policy and Law*, 26(2), 249-266.

Niveau, G, & Dang, C. (2003). Cannabis and violent crime. *Medicine, Science, and the Law*, 43(2), 115-121.

O'Connell, T.J. & Bou-Matar, C.B. (2007). Long term marijuana users seeking medical cannabis in California (2001-2007): Demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants. *Harm Reduction Journal*, 4(16). doi:10.1186/1477-7517-4-16.

Pichardo Almanzar, N.A. (2003). Framing the user: Social constructions of marijuana users and the medical marijuana movement. Proceedings of the Hawaii International Conference on Social Sciences. June 12-15, Honolulu, Hawai'i. Retrieved on September 8, 2009, from <http://www.hicsocial.org/Social2003Proceedings/Nelson%20A.%20Pichardo%20Almanzar.pdf>.

Reece, A.S. (2009). Chronic toxicology of cannabis. *Clinical Toxicology (Philadelphia)*, 47(6), 517-524.

Richer, I. & Bergeron, J. (2009). Driving under the influence of cannabis: Links with dangerous driving, psychological predictors, and accident involvement. *Accident Analysis & Prevention*, 41(2), 299-307.

Substance Abuse and Mental Health Services Administration (2008). *Drug Abuse Warning Network, 2006: National estimates of drug-related emergency department visits*. DAWN Series D-30, DHHS Publication No. (SMA) 08-4339, Rockville, MD.: U.S. Department of Health and Human Services.

Schwab, I.R., Chavis, P.S., Husted, R., & Liegner, J.T. (2003). Marijuana in the treatment of glaucoma. Retrieved on August 31, 2009, from <http://www.eyecareamerica.org/eyecare/treatment/alternative-therapies/marijuana-glaucoma.cfm>.

Seligman, K. (2007, April 22). Connoisseurs of cannabis: Like fine wine, growing medicinal weed has become so specialized as to inspire tastings and a new vocabulary. *San Francisco Chronicle*. Retrieved on September 10, 2009 at <http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2007/04/22/CMGK8OSSAA1.DTL#ixzz0QpoSMKSH>.

Sewell, R.A., Ranganathan, M., & D'Souza, D.C. (2009). Cannabinoids and psychosis. *International Review of Psychiatry*, 21(2), 152-162.

Smith, D. & Lauder, T.S. (2009, September 10). Where's the weed? Mapping L.A.'s marijuana dispensaries. *Los Angeles Times*. Retrieved on September 11, 2009 from <http://www.latimes.com/news/la-me-weed11-2009sep11.0.3123586.story>.

Tramèr, M.R., Carroll, D., Campbell, F.A., Reynolds, D.J., Moore, R.A., & McQuay, H.J. (2001). Cannabinoids for control of chemotherapy induced nausea and vomiting: Quantitative systematic review. *British Medical Journal*, 323(7303), 16-21.

U.S. Food & Drug Administration (2006, April 20). Inter-agency advisory regarding claims that smoked marijuana is a medicine. Retrieved on September 8, 2009 from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108643.htm>.

Verdoux, H. & Tournier, M. (2004). Cannabis use and risk of psychosis: An etiological link? *Epidemiologia e Psichiatria Sociale*, 13(2), 113-119.

Zammit, S., Moore, T.H.M., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., et al. (2008). Effects of cannabis use on outcomes of psychotic disorders: Systematic review. *British Journal of Psychiatry*, 193(5), 357-363.