

Marijuana as Medicine

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In 1999, the Institute of Medicine (IOM) issued a well received report, *Marijuana and Medicine: Assessing the Science Base*. The report concluded that "Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however is a crude THC delivery system that also delivers harmful substances."

The IOM made six recommendations, including:

- Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.
- Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trial should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.
- 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 specified use.

The report acknowledged that there is no clear alternative for people suffering from chronic conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as n-of-1 clinical trials, in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of risks and benefits of marijuana use under such conditions. We recommend these n-of-1 clinical trials using the same oversight mechanism as that proposed in the above recommendations.⁽¹⁾

AMA Report A01: Medical Marijuana

To update its 1997 policy on the subject, and in response to the intensifying public debate, in 2001 the American Medical Association's Council on Scientific Affairs undertook a review of the literature and produced a report. *Medical Marijuana* (A-01) was presented to the House of Delegates and its recommendations were adopted as AMA policy. The report reviews State initiatives concerning medical marijuana; current regulations and efforts to support research; pharmacology of marijuana; the major proposed medical uses of marijuana, analgesic effects of THC and smoked marijuana; adverse

effects of marijuana; progress on settling the debate on marijuana as medicine. Lastly, the report enumerated five recommendations.

Changes Since Release of the 1999 IOM Report and the AMA Report on Medical Marijuana (A-01)

From 2001 to 2007, approximately 115 articles on the subject of medical marijuana were published. They reveal little change since the publication of the Institute of Medicine Report in 1999. The primary proposed medical uses of marijuana remain as an antiemetic for severe nausea/vomiting associated with cancer chemotherapy or other causes; treatment for intractable hiccups; for cachexia associated with AIDS or cancer; spasticity secondary to neurologic diseases such as multiple sclerosis; pain management, especially neuropathic pain; and rheumatoid arthritis.⁽²⁾ Results of the various studies were mixed. In some, there was not objective improvement but patients described subjective relief. In others, there was objective improvement and in others improvement was less than with existing medications. Emerging possibilities for cannabinoids could include neuroprotection, anti-inflammation, immunomodulation, and modulation of glial cells.⁽³⁾ Possible new agonist agents acting at cannabinoid receptors may be able to dissociate therapeutic effects from psychoactive effects.

Risk factors for marijuana include adverse psychiatric, cardiovascular, respiratory, and immunologic events. Recent studies suggest both an increased risk of schizophrenia⁽⁴⁻⁶⁾ and doubling of grey matter loss in schizophrenia associated with marijuana use.⁽⁷⁾

Future delivery forms are a transdermal patch, nasal patch, and a metered dose inhaler. THC without other cannabinoids or carcinogens is currently available in the United States as an oral tablet in the form of dronabinol (Marinol, a Schedule 3 agent.) Many studies report that oral marijuana should not be first line in medications; however it should be part of the available arsenal. Most recommend further clinical trials to test effectiveness.⁽⁸⁾

A metered dose inhaler containing THC and cannabidiol, a non-psychoactive cannabinoid (Sativex), has been approved in Canada for treatment of some symptoms of multiple sclerosis and is being studied in the United States for chronic pain secondary to cancer.

Since the discovery and cloning of cannabinoid receptors (CB1 and CB2) in the 1990's and a number of endogenous ligands, interest in the endocannabinoid system has markedly expanded. Cannabinoids interact with a number of other receptor systems, appear to affect a number of bodily functions and may have efficacy in various medical conditions for which current treatments may be inadequate. There are more than 460 active chemicals and over 60 unique cannabinoids in the cannabis sativa plant. However, CB1 receptor agonists may have undesirable CNS impact and requisite doses may not be attainable before excessive side effects develop.

Note: The authors of the APA Position Statement reviewed 115 articles that were published from 2001-2007. Search engines used were Medline, PsychLit, Ovid, GoogleScholar, & UpToDate. Keywords used were medical marijuana, medical cannabis, medical THC, medical uses of marijuana, cannabis, and THC.

All are published after the publication of the IOM report. The vast majority of articles used cannabis preparations via the oral route. Some used just THC, others an extract from the cannabis sativa plant.

REFERENCES

1. Marijuana and Medicine: Assessing the Science Base by Institute of Medicine, Janet E. Joy, Jr. Stanley J. Watson, and Jr. John A. Benson (Hardcover - Jul 15, 1999), p. 177-179
2. Abrams, D.I., Jay, C., Petersen, K., Shade, S., Vizoso, H., Reda, H., Benowitz, N., Rowbotham, M. The Effects of Smoked Cannabis in Painful Peripheral Neuropathy and Cancer Pain Refractory to Opioids. Proceedings of the International Association of Cannabis as Medicine, Cologne, 2003, p.28.
3. Drysdale AJ, Platt B. Cannabinoids: mechanisms and therapeutic applications in the CNS. *Curr Med Chem*. 2003 Dec;10(24):2719-32. Review. PMID: 14529462 [PubMed - indexed for MEDLINE] 70: Related Articles, Related Articles by Review, LinksMüller-Vahl KR.
4. Moore, T.H.M., Zammit, S., Lingford-Hughes, et al Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review. *Lancet* 2007, 370: 319-28
5. Nordentoft, M., Hjorthoj, C. Cannabis Use and Risk of Psychosis in Later Life. *Lancet* 2007; 370:293-94
6. Gonzalez-Pento, A., Vega, P., Ibanez, B. et al Impact of Cannabis and Other Drugs on Age at Onset of Psychosis. *J. Clin Psychiatry* 2008; 69: 1210-16
7. Rais, M., Calin, W., Van Haren, N. Excessive Brain Volume Loss Over Time in Cannabis- Using First Episode Schizophrenic Patients *Am J. Psychiatry* 2008; 165: 490-496
8. Medical marijuana: emerging applications for the management of neurologic disorders. *Phys Med Rehabil Clin N Am*. 2004 Nov; 15(4):943-54, ex.