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Working to Reform Marijuana Laws

Marinol Versus Natural Cannabis

Pros, Cons and Options for Patients

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Updated August 11, 2005

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INTRODUCTION

Marinol[1] (dronabinol) is the only US FDA-approved synthetic cannabinoid. It is often marketed as a legal pharmaceutical alternative to natural cannabis.

Marinol is manufactured as a gelatin capsule containing synthetic delta-9-tetrahydrocannabinol (THC) in sesame oil. It is taken orally and is available in 2.5mg, 5mg and/or 10mg dosages. Marinol may be prescribed for the treatment of cachexia (weight loss) in patients with AIDS and for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Despite FDA approval,2 Marinol typically provides only limited relief to select patients, particularly when compared to natural cannabis and its cannabinoids. Marinol should remain a legal option for patients and physicians; however, federal and state laws should be amended to allow for those patients who are unresponsive to synthetic THC the ability to use natural cannabis and its cannabinoids as a medical therapy without fear of arrest and/or criminal prosecution. By prohibiting the possession and use of natural cannabis and its cannabinoids, patients are unnecessarily restricted to use a synthetic substitute that lacks much of the therapeutic efficacy of natural cannabis.

I. MARINOL LACKS SEVERAL OF THE THERAPEUTIC COMPOUNDS AVAILABLE IN NATURAL CANNABIS

Chemical compounds in cannabis, known as cannabinoids, are responsible for its numerous therapeutic benefits. Scientists have identified 66 naturally occurring cannabinoids.[3]

The active ingredient in Marinol, synthetic delta-9-tetrahyrdocannabinol (THC), is an analogue of one such compound, THC. However, several other cannabinoids available in cannabis -- in addition to naturally occurring terpenoids (oils) and flavonoids (phenols) -- have also been clinically demonstrated to possess therapeutic utility. Many patients favor natural cannabis to Marinol because it includes these other therapeutically active cannabinoids.

For example, cannabidol (CBD) is a non-psychoactive cannabinoid that has been clinically demonstrated to have analgesic, antispasmodic, anxiolytic, antipsychotic, antinausea, and anti-rheumatoid arthritic properties.[4]

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[1] Marinol is produced and marketed by Unimed Pharmaceuticals, a subsidiary of Solvay Pharmaceuticals.

[2] The FDA approved Marinol in 1985 as a Schedule II controlled substance. By definition, Schedule II drugs adhere to the following criteria: (A) The drug has a high potential for abuse; (B) The drug has a currently accepted medical use in treatment in the United States; (C) Abuse of the drug may lead to severe psychological or physical dependence. In 1999, Marinol was downgraded to a Schedule III controlled substance. By definition, Schedule III drugs adhere to the following criteria: (A) The drug has a potential for abuse less than Schedule I and Schedule II drugs; (B) The drug has a currently accepted medical use in treatment in the United States; (C) Abuse of the drug may lead to moderate or low physical dependence or high psychological dependence.

[3] National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and medicine: Assessing the Science Base*. National Academy Press: Washington, DC. p. 25: Table 1.5: Cannabinoids Identified in Marijuana.

[4] R. Mechoulam et al. 2003. Cannabidiol: an overview of some pharmacological aspects. *Neuroscience Letters* 346: 61-64; J. McPartland and E. Russo. 2002. Cannabis and cannabis extracts: greater than the sum of their parts. *Journal of Cannabis Therapeutics* 1: 103-132; A. Zuardi and F Guimaraes. Cannabidiol as an anxiolytic and antipsychotic. In: M. Mathre (Ed): *Cannabis in medical practice: a legal, historical and pharmacological overview of therapeutic use of*

Animal and human studies have shown CBD to possess anti-convulsant properties, particularly in the treatment of epilepsy.[5] Natural extracts of CBD, when administered in combination with THC, significantly reduce pain, spasticity and other symptoms in multiple sclerosis (MS) patients unresponsive to standard treatment medications.[6]

Clinical studies also demonstrate CBD to be neuroprotective against glutamate neurotoxicity[7] (i.e. stroke), cerebral infarction[8] (localized cell death in the brain), and ethanol-induced neurotoxicity,[9] with CBD being more protective against glutamate neurotoxicity than either ascorbate (vitamin C) or alpha-tocopherol (vitamin E).[10] Clinical trials have also shown CBD to possess anti-tumoral properties,[11] inhibiting the growth of glioma (brain tumor) cells in a dose dependent manner and selectively inducing apoptosis (programmed cell death) in malignant cells.[12]

Additional cannabinoids possessing clinically demonstrated therapeutic properties include: cannabinol (anticonvulsant[13] and anti-inflammatory[14] activity); cannabichromine (anti-inflammatory[15] and

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marijuana. McFarland Press: 1997: 133-141.

5 P. Consroe and S. Snider. Therapeutic Potential of Cannabinoids in Neurological Disorders. In: R. Mechoulam (Ed): *Cannabinoids as Therapeutic Agents*. CRC Press: 1986 21-51; E. Carlini and J. Cunha. 1981. Hypnotic and antiepileptic effects of cannabidiol. *Journal of Clinical Pharmacology*. 21: 417S-427S; J. Cunha et al. 1980. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 21: 175-185.

6 D. Wade et al. 2004. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Multiple Sclerosis* 10: 339-340; D. Wade et al. 2003. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Journal of Clinical Rehabilitation* 17: 21-29.

7 A. Hampson et al. 1998. Cannabidiol and THC are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences* 95: 8268-8273.

8 K. Mishima et al. 2005. Cannabidiol Prevents Cerebral Infarction. *Stroke* 36: 1077-1082.

9 C. Hamelink et al. 2005. Comparison of cannabidiol, antioxidants, and diuretics in reversing binge ethanol-induced neurotoxicity. *Journal of Pharmacology and Experimental Therapeutics* (electronically published May 5, 2005, ahead of printing).

10 A. Hampson, et al. 1998. Cannabidiol and THC are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences.*

11 H. Patsos et al. 2005. Cannabinoids and cancer: potential for colorectal cancer therapy. *Biochemical Society Transactions*. 33: 712-714; M. Guzman. 2003. Cannabinoids: potential anticancer agents. *Nature Reviews Cancer* 3: 745-755.

12 P. Massi et al. 2004. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. *Journal of Pharmacology and Experimental Therapeutics* 308: 838-845; G. Carter et al. 2004. Medical marijuana: emerging applications for the management of neurologic disorders. *Physical Medicine and Rehabilitation Clinics of North America* 15: 943-954.

13 C. Turner et al. 1980. Constituents of *Cannabis sativa* L.: A review of the natural constituents. *Journal of Natural Products* 43: 169-304.

antidepressant[16] activity); and cannabigerol (anti-tumoral[17] and analgesic[18] activity). Natural cannabis' essential oil components (terpenoids) exhibit anti-inflammatory properties[19] and its flavonoids possess antioxidant activity.[20] Emerging clinical evidence indicates that cannabinoids may slow disease progression[21] in certain autoimmune and neurologic diseases, including multiple sclerosis[22] (MS), Amyotrophic Lateral Sclerosis[23] (Lou Gehrig's disease) and Huntington's Disease.[24]

Clinical data indicate that the synergism of these compounds is likely more efficacious[25] than the administration of synthetic THC alone.[26] For example, McPartland and Russo write: "Good evidence shows that secondary compounds in cannabis may enhance beneficial effects of THC. Other cannabinoid and non-cannabinoid compounds in herbal cannabis ... may reduce THC-induced anxiety, cholinergic deficits, and immunosuppression. Cannabis terpenoids and flavonoids may also increase cerebral blood flow, enhance

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[14] F. Evans. 1991. Cannabinoids; the separation of central from peripheral effects on a structural basis. *Planta Medica* 57: S60-S67.

[15] P. Wirth et al. 1980. Anti-inflammatory properties of cannabichromene. *Life Science* 26: 1991-1995.

[16] R. Deyo and R. Musty. A cannabichromene (CBC) extract alters behavioral despair on the mouse tail suspension test of depression. In: International Cannabinoid Research Society (Ed.) *2003 Symposium on the Cannabinoids*. ICRS: 2003.

[17] S. Baek et al. 1998. Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells. *Archives of Pharmacal Research* 21: 353-356.

[18] J. McPartland and E. Russo. 2002. Cannabis and cannabis extracts: greater than the sum of their parts. *Journal of Cannabis Therapeutics.*

[19] Ibid.

[20] Ibid.

[21] Society for Neuroscience. "Marijuana-like compound may aid array of debilitating conditions ranging from Parkinson's Disease to pain." October 26, 2004. <http://apu.sfn.org/content/AboutSFN1/NewsReleases/am2004_cannabinoids.html>

[22] G. Pryce et al. 2003. Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. *Brain*. 126: 2191-2202.

[23] C. Raman et al. 2004. Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid. *Amyotrophic Lateral Sclerosis & Other Motor Neuron Disorders* 5: 33-39.

[24] I. Lastres-Becker et al. 2003. Effects of cannabinoids in the rat model of Huntington's disease generated by an intrastraital injection of malonate. *Neuroreport* 14: 813-816.

[25] E. Williamson. 2001. Synergy and other interactions in phytomedicines. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 8: 401-409.

[26] A. Holdcroft. 2001. Cannabinoids: from plant to patient. *Investigative Drugs Journal*. 4: 773-775. (See specifically: Abstract: "The active constituents of cannabis, predominantly cannabinoids and possibly flavonoids, are more effective than a single cannabinoid. ... Government ... clinical trials of cannabis ... should enable evidence to be presented to regulatory bodies documenting the medicinal uses of standardized cannabis plant material.")

cortical activity, kill respiratory pathogens, and provide anti-inflammatory activity."[27] In an *in vitro* model of epilepsy, natural cannabis extracts performed better than THC alone.[28] In human trials, patients suffering from multiple sclerosis experienced greater symptomatic relief from sublingual natural cannabis extracts than from the administration of oral THC.[29] In 2005, Health Canada approved the oral spray Sativex[30] -- which contains precise ratios of the natural cannabinoid extracts THC and CBD, among other compounds -- for prescription use for MS-related symptoms.[31]

II. MARINOL IS MORE PSYCHOACTIVE THAN NATURAL CANNABIS

Patients prescribed Marinol frequently report that its psychoactive effects are far greater than those of natural cannabis. Marinol's adverse effects include: feeling "high," drowsiness, dizziness, confusion, anxiety, changes in mood, muddled thinking, perceptual difficulties, coordination impairment, irritability, and depression.[32] These psychoactive effects may last four to six hours.[33] About one-third of patients prescribed Marinol report experiencing one or some of these adverse effects.[34]

Marinol's oral route of administration is responsible, in part, for its heightened psychoactivity compared to inhaled cannabis. Once swallowed, Marinol passes from the stomach to the small intestine before being absorbed into the bloodstream. Following absorption, Marinol passes through the liver where a significant proportion of the drug is metabolized into other chemicals.[35] One of these chemicals, 11-hydroxy-THC, may be four to five times more potent than natural THC,[36] and is produced in greater quantities.[37] Thus, patients

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[27] J. McPartland and E. Russo. 2002. Cannabis and cannabis extracts: greater than the sum of their parts. *Journal of Cannabis Therapeutics*. p. 103.

[28] The Pharmaceutical Journal. "Cannabis herb may have advantages over THC in epilepsy." July 19, 2003.

[29] Comparison of results from: D. Wade et al. 2004. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Multiple Sclerosis* (See specifically: Abstract: Spasticity VAS scores were significantly reduced by cannabis-based medicinal extracts in comparison with placebo.) and J. Zajicek et al. 2003. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis. *Lancet*. 362: 1517-26 (See specifically: Abstract: Treatment with [oral cannabis extract or THC] did not have a beneficial effect on spasticity.)

[30] http://www.drugdevelopment-technology.com/projects/sativex/

[31] Canada News Wire. "Sativex: Novel cannabis derived treatment for MS pain now available in Canada by prescription." June 20, 2005.

[32] *Physician's Desk Reference: 43rd edition*. Medical Economics Company. 1989: 1859-1860.

[33] *Physician's Desk Reference: 52nd edition*. Medical Economics Company. 1998: 2353-2355.

[34] National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and medicine: Assessing the Science Base*. p. 203.

[35] J. Morgan and L. Zimmer, *Marijuana Myths, Marijuana Facts: A Review of the Scientific Evidence*. The Lindesmith Center. 1997: 18-19.

[36] L. Lemberger et al. 1973. Comparative pharmacology of delta-9-THC and its metabolite 11-0H-Delta-9-THC. *Journal of Clinical Investigation* 54: 2411-2417 and M. Perez-Reyes et al. 1972. Intravenous injection in man of delta-9-

administered Marinol experience the psychoactive effects of both THC and 11-hydroxy-THC, greatly increasing the likelihood that they will suffer from an adverse psychological reaction. By comparison, only minute quantities of 11-hydroxy-THC are produced when cannabis is inhaled.[38] Moreover, Marinol lacks the compound cannabidiol, which possesses anxiolytic activity and likely modifies and/or diminishes much of THC's psychoactivity in natural cannabis.[39]

III. CANNABIS VAPORIZATION OFFERS ADVANTAGES OVER ORALLY ADMINISTERED THC

Vaporization is an alternative method of cannabis administration that holds distinct advantages over both smoking and oral administration. Cannabis vaporization suppresses respiratory toxins by heating cannabis to a temperature where cannabinoid vapors form (typically around 180-190 degrees Celsius), but below the point of combustion where noxious smoke and associated toxins (i.e., carcinogenic hydrocarbons) are produced (near 230 degrees Celsius).[40] Although a comprehensive review of cannabis and health conducted by the National Academy of Sciences Institute of Medicine found "no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use,"[41] studies have found that heavy cannabis smokers face a higher risk of contracting bronchitis and respiratory illnesses.[42] This risk is likely not due to the inhalation of cannabinoids, but rather to the exposure of noxious smoke. Because vaporization can deliver therapeutic doses of cannabinoids while reducing the users intake of pyrolytic smoke compounds, it is considered to be a preferred and likely safer method of cannabis administration than smoking.[43]

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tetrahydrocannabinol and 11-hydroxy-delta-9-tetrahydrocannabinol. *Science* 177: 633-635 as cited by J. Morgan and L. Zimmer, *Marijuana Myths, Marijuana Facts: A Review of the Scientific Evidence*.

[37] L. Growing et al. 1998. Therapeutic use of cannabis: clarifying the debate. *Drug and Alcohol Review*. 17: 445-452.

[38] Ibid; J. Morgan and L. Zimmer, *Marijuana Myths, Marijuana Facts: A Review of the Scientific Evidence*, 19.

[39] G. Carter et al. 2004. Medical marijuana: emerging applications for the management of neurologic disorders. *Physical Medicine and Rehabilitation Clinics of North America;* L. Growing et al. 1998. Therapeutic use of cannabis: clarifying the debate. *Drug and Alcohol Review;* A. Zuardi et al. 1982. Action of cannabidiol on the anxiety and other effects produced by delta-9-THC in normal subjects. *Psychopharmacology* 76: 245-250; G. Karinol et al. 1974. Cannabidiol interferes with the effects of delta-9-tetrahydrocannabinol in man. *European Journal of Pharmacology* 28: 172-177.

[40] D. Gieringer et al. 2004. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. *Journal of Cannabis Therapeutics* 4: 7-27.

[41] National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base*. p. 199; See also: M. Hashibe et al. 2005. Epidemiologic review of marijuana use and cancer risk. *Alcohol* 35: 265-275; K. Rosenblat et al. 2004. Marijuana use and risk of oral squamous cell carcinoma. *Cancer Research* 64: 4049-4054; D. Ford et al. 2001. Marijuana use is not associated with head, neck or lung cancer in adults younger than 55 years: Results of a case cohort study. In: National Institute on Drug Abuse (Eds) *Workshop on Clinical Consequences of Marijuana: Program Book*. National Institutes of Health: Rockville, MD: p. 10.

[42] M. Polen et al. 1993. Health care use by frequent marijuana smokers who do not smoke tobacco. *Western Journal of Medicine* 158: 596-601; D. Tashkin. 1993. Is frequent marijuana smoking hazardous to health? *Western Journal of Medicine* 158: 635-637.

[43] D. Gieringer et al. 2004. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. *Journal of Cannabis Therapeutics.*

In practice, cannabis vaporization offers considerable advantages over oral THC consumption. While the oral ingestion of Marinol avoids the potential risks of smoking, it has other significant drawbacks. Because of synthetic THC's poor bioavailability, only 5-20 percent of an oral dose ever reaches the bloodstream[44] and the drug may not achieve peak effect until four hours after dosing.[45] Moreover, because Marinol is metabolized slowly, its therapeutic and psychoactive effects may be unpredictable and vary considerably, both from one person to another, and in the same person from one episode of use to another.[46] By contrast, cannabis vaporization delivers cannabinoids to the bloodstream almost instantaneously.[47] Vaporization's rapid onset also allows patients to self regulate their dosage of cannabinoids by immediately ceasing inhalation when/if their psychoactive effects become unpleasant.[48] After oral administration of Marinol, patients have no choice but to experience the full psychoactive effects of the dose consumed. These dysphoric effects may last several hours.

Because of its rapid onset, vaporized cannabis is more desirable than Marinol for patients requiring a fast-acting therapeutic agent, such as those combating oncoming attacks of nausea, seizures or muscle spasms. Cannabis vaporization also offers a unique advantage to patients suffering from nausea and vomiting because it allows them an alternative delivery route to swallowing. Cancer and HIV/AIDS patients often report that their stomachs cannot hold down Marinol capsules during bouts of severe nausea[49] and many rely on natural cannabis and cannabinoids for symptom control.[50] In a 1994 survey of oncologists, respondents ranked synthetic THC ninth on a list of available antiemetic medications.[51] In another survey of oncologists, 44 percent of respondents said that they believed natural cannabis to be more efficacious than oral synthetic THC; only 13 percent of respondents rated Marinol more effective.[52] A 1997 survey of physicians found that a

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[44] National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base*. p. 203; L. Growing et al. 1998. Therapeutic use of cannabis: clarifying the debate. *Drug and Alcohol Review*.

[45] National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base*. p. 203.

[46] S. Calhoun et al. 1998. Abuse potential of dronabinol. *Journal of Psychoactive Drugs*. 30: 187-196; J. Morgan and L. Zimmer, *Marijuana Myths, Marijuana Facts: A Review of the Scientific Evidence*, p. 19.

[47] Ibid; National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base.* "The poor solubility of Marinol in aqueous solutions and its high first-pass metabolism in the liver account for its poor bioavailability; only 10-20% of an oral dose reaches the systemic circulation. The onset of action is slow; peak concentrations are not attained until two to four hours after dosing. In contrast, inhaled marijuana is rapidly absorbed. ... Variations in individual responses is highest for oral THC and bioavailability is lowest."

[48] L. Growing et al. 1998. Therapeutic use of cannabis: clarifying the debate. *Drug and Alcohol Review*.

[49] Of Marinol's patient population, only about 10 percent use it to combat cancer-related nausea. National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base*. p. 204.

[50] E. Woolridge et al. 2005. Cannabis use in HIV for pain and other medical symptoms. *Journal of Pain and Symptom Management* 29: 358-67.

[51] R. Schwartz and R. Beveridge. 1994. Marijuana as an antiemetic drug: how useful today. Opinions from clinical oncologists. *Journal of Addictive Diseases* 13: 53-65.

[52] R. Doblin and M. Kleiman. 1991. Marijuana as an anti-emetic medicine: a survey of oncologists' attitudes and experiences. *Journal of Clinical Oncology* 19: 1275-1290.

majority preferred megestrol acetate over Marinol as an appetite stimulant in patients with HIV/AIDS.[53]

As a result of Marinol's slow onset and poor bioavailablity, scientists are now in the process of developing a new formulation of pulmonary dronabinol, delivered with a pressurized metered dose inhaler.[54] In a Phase I study, pulmonary Marinol delivered via an inhaler provided rapid systemic absorption. Unlike oral synthetic THC, it's possible that pulmonary Marinol "could offer an alternative for patients when a fast onset of action is desirable."[55] However, FDA approval of pulmonary Marinol and/or its inhaler remains years away. Sativex, an oral cannabis spray consisting of natural cannabinoid extracts, has greater bioavailability and is faster acting than oral synthetic THC. Clinical trials comparing its bioavailability and time of peak onset compared to vaporized cannabis have not been performed, though anecdotal reports indicate that vaporized cannabis and its cannabinoids likely possess greater bioavailability and are faster acting than the Sativex spray.

IV. MARINOL IS MORE EXPENSIVE THAN NATURAL CANNABIS

Synthetic THC is a costly and difficult compound to manufacture.[56] Much of this cost is passed on to the patient consumer, particularly if the full cost of Marinol (approximately $200 to $800 per month,[57] depending on the dosage) is borne out of pocket. Patients, particularly those with chronic conditions, often report that Marinol's market cost limits their use of the drug.[58] Doctors also report that Marinol's high cost dissuades them from prescribing it to patients. In one survey of HIV/AIDS specialists, among respondents who had never prescribed Marinol to their patients, 33 percent cited the high cost of the drug as the reason.[59] Natural cannabis, even at its inflated black market value, often remains far less costly for patients than oral synthetic THC.[60]

V. PATIENTS ULTIMATELY PREFER NATURAL CANNABIS TO MARINOL

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[53] National Institutes of Health. 1997. *Report of the Workshop on the Medical Utility of Marijuana*. Washington, DC as cited by L. Growing et al. 1998. Therapeutic use of cannabis: clarifying the debate. *Drug and Alcohol Review*.

[54] Medical News Today. "New synthetic delta-9-THC Inhaler offers safe, rapid delivery, Phase I study." April 17, 2005.

[55] Ibid.

[56] Presentation of Unimed Pharmaceuticals Senior Vice President Robert Dudley before the National Academy of Sciences, Institute of Medicine. Washington, DC: February 24, 1998.

[57] National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base*. p. 207; Morgan and L. Zimmer, *Marijuana Myths, Marijuana Facts: A Review of the Scientific Evidence*, p. 21; Medical Marijuana ProCon.org <http://www.medicalmarijuanaprocon.org/pop/cost.htm>

[58] National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base*. p. 206.

[59] L. Growing et al. 1998. *Therapeutic Uses of Cannabis*. Drug and Alcohol Services Council: South Australia.

[60] National Academy of Sciences, Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base*. p. 207; Medical Marijuana ProCon.org <http://www.medicalmarijuanaprocon.org/pop/cost.htm>

In the 1970s and 1980s, several states conducted patient trials[61] of natural cannabis' effectiveness as an anti-emetic in cancer patients unresponsive to conventional therapies. Some state protocols allowed patients to choose between inhaled cannabis[62] and synthetic THC. In those studies which compared natural cannabis to dronabinol, inhaled cannabis was equal to or better than the oral administration of synthetic THC.[63]

For example, researchers at the Tennessee Board of Pharmacy found a "23 percent higher success rate among those patients smoking than among those patients administered THC capsules" in the treatment of nausea and/or vomiting associated with cancer chemotherapy.[64]

Researchers in New Mexico observed similar findings. "When the routes of [drug] administration were analyzed separately, it was found that inhalation was far superior to ingestion: 90.39 percent of the patients in the group that inhaled the marijuana showed improvement while only 59.65 percent of the patients in the group that orally ingested the delta-9-THC showed improvement," they concluded.[65]

Researchers at the California Board of Pharmacy found that inhaled cannabis and oral THC produced similar results in patients. However, physicians still rated natural cannabis as slightly more effective than oral THC as an anti-emetic.[66]

A 1988 New York State pilot study comparing inhaled cannabis to oral THC in cancer chemotherapy patients who were unresponsive to standard antiemetic agents found: "Twenty-nine percent of patients who failed oral THC responded to the cigarette form. ... Our results demonstrate that inhalation marijuana is an effective therapy for the treatment of nausea and vomiting due to cancer chemotherapy."[67]

Today, several patient populations continue to use natural cannabis and its cannabinoids in large numbers despite its illegality and the availability of Marinol. A 2005 British survey of more than 500 HIV/AIDS patients found that one-third of respondents use natural cannabis for symptomatic relief, with more than 90 percent of

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[61] State research trials regarding natural cannabis were discontinued by 1985, after the FDA approved Marinol.

[62] The cannabis distributed in these trails was manufactured and provided by the US National Institute on Drug Abuse (NIDA). Cannabis was provided to patients in the form of a cigarette.

[63] R. Musty and R. Rossi. 2001. Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: a review of state clinical trials. *Journal of Cannabis Therapeutics*. 1: 29-56. "The data reviewed here suggested that the inhalation of THC appears to be more effective than the oral route. ... Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used THC capsules experienced 76-88% relief."

[64] Board of Pharmacy, State of Tennessee. 1983. *Annual Report: Evaluation of Marijuana and Tetrahydrocannabinol in Treatment of Nausea and/or Vomiting Associated with Cancer Therapy Unresponsive to Conventional Anti-Emetic Therapy: Efficacy and Toxicity*. p. 5.

[65] Behavioral Health Services Division. 1983. *The Lynn Pierson Therapeutic Research Program: A Report on Progress to Date*. Health and Environment Department: New Mexico. p. 4.

[66] California Research Advisory Panel. 1986. *Seventeenth Annual Report of the Research Advisory Panel*, p. 9-10.

[67] V. Vinciguerra et al. 1988. Inhalation marijuana as an antiemetic for cancer chemotherapy. *New York State Journal of Medicine* 88: 525-527.

them reporting that it improves their appetite, muscle pain and other symptoms.[68] A previous US survey found that approximately one out of four patients with HIV had used natural cannabis medicinally in the past month.[69]

Cannabis use is also prevalent among patients with neurologic disorders. Nearly four out of ten Dutch patients with prescriptions for "medical grade cannabis" (cannabis provided by Dutch pharmacies with a standardized THC content of 10.2 percent) use it to treat MS or spinal cord injuries, according to survey data published in 2005 in the journal *Neurology*.[70] Perceived efficacy is greater among respondents who inhale cannabis versus those who ingest it orally, the study found.[71]

A 2002 British survey of MS patients found that 43 percent of respondents used natural cannabis therapeutically, with about half admitting they used it regularly.[72] Seventy-six percent said they would do so if cannabis were legal.[73] A Canadian survey of MS patients found that 96 percent of respondents were "aware cannabis was potentially therapeutically useful for MS and most (72 percent) supported [its] legalization for medicinal purposes."[74] Sixteen percent of respondents answered that they use natural cannabis for medical purposes to treat symptoms of anxiety/depression, spasticity and chronic pain.[75]

A more recent Canadian survey published in *Neurology* reported that 14 percent of MS[76] patients and 21 percent of respondents with epilepsy had used medical cannabis in the past year.[77] Among epileptics, twenty-four percent of respondents said that they believed that cannabis was an effective therapy for the disease.[78] A 2002 survey of patients with Parkinson's Disease (PD) found that 25 percent of respondents had tried cannabis, with nearly half of those saying that it provided them symptomatic relief.[79]

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[68] E. Woolridge et al. 2005. Cannabis use in HIV for pain and other medical symptoms. *Journal of Pain and Symptom Management*.

[69] D. Prentiss et al. 2004. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *Journal of Acquired Immune Definiciency Syndromes* 35: 38-45

[70] R. Gorter et al. 2005. Medical use of cannabis in the Netherlands. *Neurology* 64: 917-919.

[71] Ibid.

[72] Reuters News Wire. "Marijuana helps MS patients alleviate pain, spasms." August 19, 2002.

[73] Ibid.

[74] S. Page et al. 2003. Cannabis use as described by people with multiple sclerosis. *Canadian Journal of Neurological Sciences* 30: 201-205.

[75] Ibid.

[76] A. Clark et al. 2004. Patterns of cannabis use among patients with multiple sclerosis. *Neurology* 62: 2098-2100.

[77] D. Gross et al. 2004. Marijuana use and epilepsy. *Neurology* 62: 2095-2097.

[78] Ibid.

[79] Reuters News Wire. "Pot may ease Parkinson's symptoms -- Czech study." November 13, 2002.

CONCLUSION

Oral synthetic THC, legally available by prescription as Marinol, often provides only limited relief to a select group of patients, particularly when compared to natural cannabis and its cannabinoids. Patients often experience minimal relief from Marinol and many experience unwanted side effects. In addition, many physicians are hesitant to prescribe the drug, and some patients are unable to afford it. Despite Marinol's legality, many patient populations continue to risk arrest and criminal prosecution to use natural cannabis medically, and most report experiencing greater therapeutic relief from it.

The active ingredient in Marinol is a synthetic analogue of only one of the compounds in cannabis that is therapeutically beneficial to patients. By prohibiting the possession and use of natural cannabis and its cannabinoids, patients are unnecessarily burdened to use a synthetic substitute that lacks much of the therapeutic efficacy of natural cannabis and its cannabinoids.

Marinol should remain a legal option for patients and physicians and the development of additional cannabis-based pharmaceuticals should be encouraged. However, federal and state laws should be amended to allow for those patients who are unresponsive to synthetic THC, or simply desire an alternative to oral dronabinol, the ability to use natural cannabis and its cannabinoids as a legal medical therapy without fear of arrest and/or criminal prosecution.