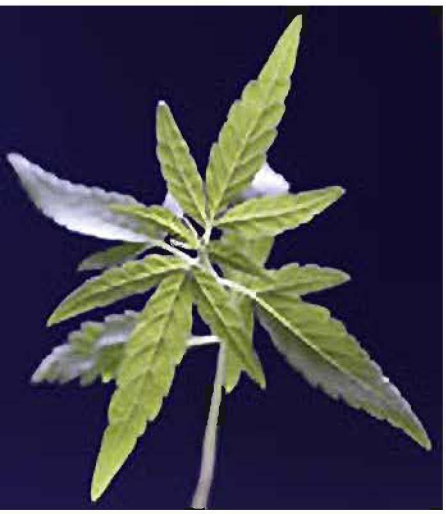
THE JOURNAL OF GLOBAL DRUG POLICY AND PRACTICE



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Marijuana: The present challenge and the future of cannabinoid research

Welcome to the inagural issue of the Journal of Global Drug Policy and Practice, a joint effort of the Institute on Global Drug Policy and the International Scientific and Medical Forum on Drug Abuse. The Journal of Global Drug Policy and Practice is an international, open access, peer-reviewed, online journal with the goal of bridging the information gap on drug policy issues between the medical/scientific community, policymakers and the concerned lay public.

Edited by Eric A. Voth, MD, FACP, and David A. Gross, MD, FAAP, our intended readership includes clinicians, clinical researchers, policymakers, prevention specialists and the interested public.

IN THIS ISSUE

THE JOURNAL OF
GLOBAL DRUG POLICY AND PRACTICE

Marijuana and cannabinoid research: Current status and future potential.

Eric A. Voth, MD, FACP

Abstract

Unlike any other illegal drug of abuse, efforts undertaken by pro-marijuana advocates to legalize marijuana have attempted to exploit alleged medicinal applications to gain legal status and public acceptance. In the process, the accepted legal channels for bringing drugs to market have become trampled and circumvented, and it has been extremely difficult for the professional and lay public to sort the "wheat from the chaff."

A historical perspective will review the efforts to legitimize marijuana to date, the status of research involving cannabinoid and related substances will be examined, the legal status of cannabis will be reviewed, and the marijuana legalization campaign will be scrutinized.

Historical perspective

Ancient uses of marijuana (cannabis sativa) are considered by marijuana advocates as evidence to support medical and recreational uses today. The historical uses of marijuana cited by Grinspoon (1) include such cultures as India, Asia, the Middle East, South Africa, and South America and are considered by the medical excuse marijuana movement as evidence of appropriate medical uses of the drug. The Chinese allegedly used marijuana to "quicken the mind, induce sleep, cure dysentery, stimulate appetite, relieve headaches, and cure venereal disease." One reference from 1860 states marijuana provided beneficial medical effects "without interfering with the actions of the internal organs." Such folk medicine applications of marijuana from the 1700s and 1800s are referenced by Grinspoon as evidence justifying modern medical applications. The field of medicine in those earlier years was fraught with potions and herbal concoctions. Many of those were absolutely useless, or conversely were harmful to unsuspecting subjects.

The movement to legalize marijuana has existed in various forms since the 1970s. Throughout that time, the medical excuse for marijuana has become a centerpiece for the marijuana legalization movement. Several states have been forced to deal with full marijuana legalization campaigns along with numerous legal and ballot initiatives making marijuana accessible for alleged medical applications.

This author has previously reviewed the literature concerning the medicinal use of marijuana and contends that the medical excuse marijuana movement creates a medical "Pandora's box" creating numerous regulatory, medical, scientific, and ethical challenges (2,3). One previous work (2) has additionally traced the organization and financing of the medical excuse movement to a core of marijuana legalization advocates. This movement is funded largely by billionaire currency magnate, George Soros. Most notably, the medical excuse movement is responsible for fostering a "medicine by popular vote" mentality and undermining medical regulatory agencies (4). Ballot initiatives and legislative actions which bypass the FDA processes for consumer protection jeopardize the public and unwitting patients.

In 1997 the White House Office of National Drug Control Policy commissioned the National Academy of Science, Institute of Medicine (IOM) to evaluate the utility of marijuana for medicinal applications (5). One conclusion of the study determined that the challenge for future research will be to find cannabinoids which enhance therapeutic benefits while minimizing side effects such as intoxication and dysphoria. The future for medicinal applications of cannabinoids and whether cannabinoids are equal or superior to existing medicines remains to be determined, but the IOM evaluation is particularly clear on the smoking of marijuana:

> "If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but such trials could be a first step towards the development of rapid-onset, non-smoked cannabinoid delivery system."

In its attempt to advance marijuana, the marijuana lobby has moved in the opposite direction of the IOM study. The medical excuse contingent now focuses on the allegedly superior benefits of the therapeutic whole plant uses. Of course, this means that patients would be exposed to 66 cannabinoids and over 400 other substances that exist in crude herbal marijuana (6). There exists a notable lack of research in the literature on beneficial effects of this therapeutic "witches brew" of substances as compared to isolated cannabinoids. This whole-plant strategy is pivotal to the advocates' arguments that there exist some unique properties of the aggregate plant products, yet this has never been substantiated in the medical literature.

Effects of marijuana use

The negative side effect profile of marijuana far exceeds most of the other effective agents available for symptoms such as nausea and appetite stimulation. Such side effects also pose danger to those who use marijuana for intoxication as well. Chronic, daily doses of the drug would be necessary to treat many of the proposed medical conditions.

Mental, affective, and behavioral effects are the most easily recognized consequences of acute and chronic marijuana use. Concentration, motor coordination, and memory (7-11) are all adversely impacted. In an examination of college students (12), daily use of marijuana was associated with cognitive impairment of "executive functions" such as learning of lists, perseveration, and attention. In certain medical applications such as terminal cancer patients, such impairment may be less of a concern than in the daily functioning of high school and college students.

Pathologic behavior such as psychosis is also associated with marijuana use (13-15). Not surprisingly, an upsurge in marijuana-induced psychosis has been discovered in England since the marijuana laws were relaxed. This has resulted in substantial political conflict as well as a serious reconsideration of the legal status to "class B" by the Home Secretary Charles Clarke (16).
Solowij and coworkers reported that the ability to focus attention and filter out irrelevant information was progressively impaired with the number of years of use but was not related to the frequency of use (17). Solowij also determined in a separate report that even among ex-cannabis smokers, the inability to reject complex irrelevant information persisted despite a mean abstinence of two years from marijuana use (18).

Chronic marijuana use is associated with increased cerebrovascular resistance through changes mediated, in part, in blood vessels or in the brain parenchyma (19). These findings might provide a partial explanation for the cognitive deficits observed in a similar group of marijuana users. Pulsatility index, a measure of cerebrovascular resistance, and systolic velocity were significantly increased in the marijuana users vs. control subjects. These increases persisted in the heavy marijuana users after a month of monitored abstinence.

Positron scanning (20) of subjects whose mean use of marijuana was 17 times per week for the last 2 years found lower blood flow in a large region of the posterior cerebellum. Not only does this have implications on motor coordination and function but also cognition, timing, processing sensory information, and attention.

The ability to perform complex tasks, such as flying (21-22) is impaired even 24 hours after the acute intoxication phase. The association of marijuana use with trauma and intoxicated motor vehicle operation is also well established (23-28). Evaluations of the effect of marijuana on driving (29) have determined that the combination of blood alcohol concentrations (BAC) of 0.07 and marijuana at 100ug/kg gave effects similar to BAC alone of 0.09. Blood alcohol concentrations of 0.07 and marijuana levels of 200ug/kg demonstrated effects similar to a BAC alone of 0.14 when measuring reaction time, on-road performance, and vehicle following. A second, related study found that a BAC of .05 combined with moderate marijuana use caused a significant drop in the visual search frequency.

In young smokers, the consequences of acute cardiovascular effects may be minimal. On the other hand, Mittleman et al found that risk of a myocardial infarction (MI) within one hour of use is increased by 4.8 times compared to periods of non-use. This type of effect along with the tachycardia caused by marijuana would limit use in elderly individuals or those suffering cardiac disease (30).

Despite arguments from the marijuana advocates to the contrary, marijuana is a dependence-producing drug. This dependence and associated "addictive" behaviors have been well described in the marijuana literature (31-36). Marijuana dependence consists of both a physical dependence (tolerance and subsequent withdrawal) and a psychological dependence. Justinova et al (37) characterizes marijuana as highly reinforcing with a pronounced abuse potential. This is likely due at least in part to the rapid uptake of the smoked drug and may also explain the relative lack of abuse seen with oral preparations such as dronabinol (Marinol).

Withdrawal from marijuana has been induced by blockade of the CB1 receptor by rimonabant in animals (38) and has been characterized in humans (39). Marijuana withdrawal in human patients is often subtle and may be fairly benign because of the long half life and slow elimination.

The gateway effect of marijuana along with tobacco and alcohol is also well established in research (40,41). The use of cocaine and heroin is virtually always preceded by marijuana. Kandel and co-workers have pioneered research in this area and continue to find clear evidence of a gateway phenomenon (42,43). Golub contends that the importance of marijuana as a gateway drug has actually increased in recent years (44).

Respiratory difficulties associated with marijuana use preclude the inhaled route of administration as a medicine. Smoking marijuana is associated with higher concentrations of tar, carbon monoxide, and carcinogens than are found in cigarette smoking (45). Marijuana adversely impairs some aspects of lung function and causes abnormalities in the respiratory cell lines from large airways to the alveoli (46-54). Marijuana smoke causes inflammatory changes in the airways of young people that are similar to the effects of tobacco (55). In addition to these cellular abnormalities and consequences, contaminants of marijuana smoke are known to include various pathogenic bacteria and fungi (56-58). Those with impaired

immunity are at particular risk for the development of disease and infection when these substances are inhaled.

Exposure to marijuana during pregnancy (59-64) is associated with changes in size, weight, and neurologic abnormalities in the newborn. Additionally, hormonal function in both males and females is disrupted (65-69).

Substantial concern exists around what delayed and persistent effect marijuana may have on the unborn. Day and colleagues have identified a negative effect on intelligence parameters among 3 year olds when mothers used marijuana during the first and second trimesters of pregnancy (70). Dahl and coworkers have discovered sleep disruption among three year olds when exposed during pregnancy (71). Consistent with the reports of delayed performance, Fried (72) reported that children exposed in utero demonstrate increased behavioral problems, impaired language comprehension, and sustained attention and memory problems at age 4.

One of the earliest findings in marijuana research was the effect on various immune functions, which is evidenced by an inability to fight herpes infections and the discovery of a blunted response to therapy for genital warts during cannabis consumption (73,74). Evaluation of the effect of THC on NK-*k*B has suggested a possible effect on the HIV genome (75).

Future directions

Useful delivery systems for isolated or synthetic cannabinoids could include nasal sprays, metered dose inhalers, transdermal patches, and suppositories. The problem with whole plant extracts, and certainly with smoking marijuana therapeutically, remains a relative "shotgun" effect of 66 cannabinoids and a plethora of other toxic substances.

As it relates to the potential for future medicinal applications, we suggest that there exists no compelling data to begin to suggest that plant marijuana for medicinal applications provides an advantage over individual cannabinoids or other existing medicine. For the most part, positive or negative physiological effects of cannabinoids are the result of the stimulation of cannabinoid receptors CB1 (76) and CB2 (77). CB1 receptors are most prevalent in the hippocampus, amygdala, cortex, basal ganglia, and cerebellum. Thus, they have association with effects on memory, emotion, cognition, and movement. They are also present in the periaqueductal gray matter of the dorsal horn of the spinal cord responsible for pain perception (78). CB2 receptors are mostly present in peripheral tissue. CB1 receptors are sparse in the brainstem which may explain the lack of respiratory suppression seen with narcotic analgesics. Refining and isolating the natural cannabinoids, synthesizing substances which target specific CB1 or CB2 receptor groups, or selective receptor inhibition, appear to represent the future for cannabinoid research.

The cannabis plant is relatively nonselective in its stimulation of cannabinoid receptors, and thus acute use results in a variety of side effects beyond the targeted therapeutic effects, limiting potential uses (78). Yet, it is likely the CB1 receptors that mediate marijuana dependence (38).

The identification of the cannabinoid receptors has opened the door to both the development of specific agonists for use on nausea, pain, and antagonists such as the new agent Rimonabant. There still exists potential for the development of cannabinoids which have enhanced therapeutic benefits with little intoxication or toxicity such as Delta-8-THC.

The most salient response to the marijuana lobby exists in the Food and Drug Administration processes which have been developed to protect the public and should continue to do so. Keeping to their mandate, proceeding to assure both efficacy and safety is paramount without manipulation or lobbying pressure from the legalization and medical excuse advocates. As a practicing physician, this author contends that we should demand the best quality and consistency of medicine for our patients. One must then realize that with marijuana the patient is exposed to a veritable "witches brew" of substances, most of which have never been examined for harmful effects. The medical literature lacks any clear documentation of a significant body of patients who have failed all other therapies for whom marijuana actually provides the only relief.

Ballot initiatives or legislative actions which support either medical excuse marijuana or outright legalization efforts create a huge conundrum for law enforcement and medical regulatory agencies. If physicians choose to recommend marijuana for patients, they should be aware that a minimum standard of care exists (79) for care providers. Informed consent should include the myriad of medical side effects and consequences of use. Failure to inform is actionable to the same degree as lack of informed consent for other dangerous medications or procedures.

Finally, the motivation of the medical excuse marijuana movement is suspect. While it masquerades as altruism, it is a Trojan Horse which the marijuana advocates themselves have identified as a "camel's nose under the tent" to gain acceptance of marijuana. The marijuana lobby has effectively influenced the public and exploited compassion and sympathy for suffering patients to advance the cause of legal marijuana. By framing the issue so simplistically, the pro-marijuana lobby has set the stage for a cultural and social shift to ultimately achieve the legalization of marijuana and, for that matter, other illicit drugs.

References

1. **Grinspoon L, and Bakalar J B.** *Marijuana: The Forbidden Medicine*. Yale University Press 1993.

2. **Voth EA**, A peek into Pandora's box: The medical excuse marijuana controversy. J Addict Diseases 2003;22:27-46.

3. **Voth EA**, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. Ann Int Med. 1997;126:791-798.

4. **Voth EA**, Guidelines for prescribing medical marijuana West J Med2001;175:305-306. West J Med 2001;175:305-306.
http://www.ewjm.com/cgi/content/full/175/5/305

5. **Joy JE, Watson, Jr SJ, Benson JA. eds.** Marijuana and medicine: assessing the science base. Science Division of Neuroscience and Behavioral Health, Institute of Medicine. National Academy Press, Washington, D.C. 1999:178. www.nap.edu.

6. **Ross SA, Elsohly MA.** Constituents of Cannabis Sativa L. XXVIII A review of the natural constituents: 1980-1994. J. Pharm Science. 1995;4:1-10.

7. **Block R I, Wittenborn J R.** Marijuana effects on the speed of memory retrieval in the letter-matching task. *International Journal of the Addictions.* 1986;21:281-285.

8. **Leon-Carrion J.** Mental performance in long-term heavy cannabis: a preliminary report. *Psychological Reports.* 1990;67:947-952.

9. **Murray J B.** Marijuana's effects on human cognitive functions, psychomotor functions, and personality. *Journal of General Psychology.* 1986;113:23-55.

10. **Schwartz R H, Gruenwald P J, Klitzner M, and Fedio P.** Short-term memory impairment in cannabis -dependent adolescents. *AJDC.* 1989;143:1214-1219.

11. **Varma V K, Malhotra A K, Dang R, Das K, and Nehra R.** Cannabis and cognitive functions: a prospective study. *Drug and Alcohol Dependence.* 1988;21:147-152.

12. **Pope HG, Yurgelun-Todd D,** The Residual Cognitive Effects of Heavy Marijuana Use in College Students. *JAMA* 1996;275:521-527.

13. **Solomons K, Neppe V M, and Kuyl J M.** Toxic cannabis psychosis is a valid entity. *SAMJ.* 1990;78:476-481.

14. **Nahas C G.** Historical outlook of the psychopathology of cannabis.*Cannabis: Physiopathology, Epidemiology, Detection.* CRC Press.1993:95-99.

15. **Mathers D C, and Ghodse A H.** Cannabis and psychotic illness. British Journal of Psychiatry. 1992;161:648-653.

16. **Clarke.** London Times. 2006 Jan 5. Available from http://www.timesonline.co.uk/.

17. **Solowij N, Michie PT,** Fox AM, Differential Impairments of Selective Attention Due to Frequency and Duration of Cannabis Use. *Biological Psychiatry* 1995;37:731-739.

18. **Solowij N,** Do Cognitive Impairments Recover Following Cessation of Cannabis Use? *Life Sciences* 1995;5:2119-26.

19. **Ronald I. Herning, PhD, Warren E. Better, MS, Kimberly Tate, BS and Jean L. Cadet, MD** Cerebrovascular perfusion in marijuana users during a month of monitored abstinence. Neurology 2005;64:488-493.

20. **Block RI, O'Leary DS, Hichwa RD, Augustinack JC, Boles-Ponto LL, Ghoneim M M, Arndt S, Ehrhardt JC, Hurtig RH, Watkins GL, Hall JA, Nathan PE, Andreasen NC**. Cerebellar hypoactivity in frequent marijuana users. *NeuroReport* 2000;4:749-753.

21. **Leirer V O, Yesavage J A, and Morrow D G.** Marijuana carry-over effects on psychomotor performance: a chronicle of research. *Cannabis: Physiopathology, Epidemiology, Detection.* CRC press. 1993 47-60.

22. **Yesavage J A, Leirer V O, Denari M, and Hollister L E.** Carry-over effects of marijuana intoxication on aircraft pilot performance; a preliminary report. *Am. J. Psychiatry.* 1985;142:1325-1329.

23. **Brookoff D, Campbell E A, and Shaw L M.** The underreporting of cocaine-related trauma: drug abuse warning network reports vs. hospital toxicology tests. *American Journal of Public Health.* 1993;83:369-371.

24. **Gerostamoulos J., and Drummer O H.** Incidence of psychoactive cannabinoids in drivers killed in motor vehicle accidents. *Journal of Forensic Sciences.* 1993;38:649-656.

25. **Gjerde H, and Kinn G.** Impairment in drivers due to cannabis in combination with other drugs. *Forensic Science International.* 1991;50:57-60.

26. **Kirby J M, Maull K I, and Fain W.** Comparability of alcohol and drug use in injured drivers. *Southern Medical Journal.* 1992;85:800-802.

27. **Marzuk P M, et al.** Prevalence of recent cocaine use among motor vehicle fatalities in New York City.*JAMA.* 1990;263:250-256.

28. **Soderstrom C A, et al.** Marijuana and alcohol use among 1023 trauma patients. *Cannabis; Physiopathology, Epidemiology, Detection.* CRC press 1993;79-91.

29. **National Highway Traffic Safety Administration.** Marijuana and Alcohol Severely Impede Driving Performance. *Annals of Emergency Medicine*2000:35;398-399. NHTSA study-- National Highway Traffic Safety Administration. Marijuana Alcohol and Actual Driving Performance. DOT HS 808.939.

30. **Mittlemen MA, Lewis RA, Maclure M, Sherwood JB, Muller JE.** Triggering of Myocardial Infarction by Marijuana Circulation 2001;103:2805.

31. **Compton D R, Dewey W L, and Martin B R.** Cannabis dependence and tolerance production. *Advances in Alcohol and Substance Abuse.* 1990;9:129-147.

32. **Kaplan H B, Martin S S, Johnson R J, and Robbins C A.** Escalation of marijuana use: Application of a general theory of deviant behavior. *Journal of Health and Social Behavior.* 1986;27:44-61.

33. **Kaufman E, et al.** Committee on Drug Abuse of the Council on Psychiatric Services. Position statement on psychoactive substance use and dependence: update on marijuana and cocaine. *Am J Psychiatry.* 1987;144:698-702.

34. **Miller N S, and Gold M S.** The diagnosis of marijuana (cannabis) dependence. *Journal of Substance Abuse Treatment.* 1989;6:183-192.

35. **Miller N S, Gold M S, and Pottash A C.** A 12-step treatment approach for marijuana (cannabis) dependence. *Journal of Substance Abuse Treatment.* 1989;6:241-250.

36. **Schwartz R H.** Marijuana: an overview. *Pediatric clinics of North America.* 1987;34:305-317.

37. **Justinova Z, Goldberg SR, Heishman SJ, Tanda Gianluigi.** Self-administration of cannabinoids by experimental animals and human marijuana smokers. Pharmacol, Biochem, and Behavior 2005;81: 285-299.

38. **Martin BR.** The THC receptor and its antagonists. In: Nahas GG, Burks TF, eds. Drug Abuse in the Decade of the Brain. Amsterdam: IOS press;1997:139-144.

39. **Duffy A, Milin R,** Case Study: Withdrawal Syndrome in Adolescent Chronic Cannabis Users. *J. Am. Acad Child Adolesc Psychiatry.* 1996;35:1618-21.

40. **Clayton R R, Leukefeld C G.** The prevention of drug use among youth: implications of "legalization." *Journal of Primary Prevention.* 1992;12:289-302.

41. **Bailey S L, Flewelling R L, and Rachal J V.** Predicting continued use of marijuana among adolescents: the relative influence of drug-specific and social context factors. *Journal of Health and Social Behavior.* 1992; 33:51-66.

42. **Kandel DB, Davies M,** High School Students Who Use Crack and Other Drugs *Archives of General Psychiatry* 1996;53:71-80.

43. **Kandel DB, Yamaguchi K, Chen K,** Stages of Progression in Drug Involvement from Adolescence to Adulthood: Further Evidence for the Gateway Theory, *J Stud. Alcohol;1992:447-457.*

44. **Golub A, Johnson BD,** The Shifting Importance of Alcohol and Marijuana as Gateway Substances among Serious Drug Abusers *J. Stud Alcohol* 1994;55:607-614.

45. **Wu T C, et al.** Pulmonary hazards of smoking marijuana as compared with tobacco. *NEJM.* 1988;318:347-351.

46. **Gong H, et al.** Acute and subacute bronchial effects of oral cannabinoids. *Clin Pharmacol Ther.* 1984;35:26-32.

47. **Tashkin D P.** Is frequent marijuana smoking harmful to health? *Western Journal of Medicine.* 1993;158:635-637.

48. **Tashkin D P,** et. al. Respiratory status of seventy-four habitual marijuana smokers. *Chest.* 1980;78:699-706.

49.**Tashkin D P, Shapiro B J, Lee Y E, and Harper C E.** Subacute effects of heavy marijuana smoking on pulmonary function in healthy men. *NEJM.* 1976;294:125-129.

50. **Fligiel S E, Venkat H, Gong H, and Tashkin D P,** Bronchial pathology in chronic marijuana smokers: a light and electron microscopic study. *Journal of Psychoactive Drugs.* 1988;20:33-42.

51. **Tashkin D P, Simmons M, and Clark V.** Effect of habitual smoking of marijuana alone and with tobacco on nonspecific airways hyperreactivity. *Journal of Psychoactive Drugs.* 1988;20:21-25.

52. **Tilles D S, et al.** Marijuana smoking as cause of reduction in single-breath carbon monoxide diffusing capacity. *The American Journal of Medicine.* 1986;80:601-606.

53. **Barbers R G, et al.** Chemotaxis of peripheral blood and lung leukocytes obtained from tobacco and marijuana smokers. *Journal of Psychoactive Drugs.* 1988;20:15-20.

54. **Barbers R G, et al.** Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers. *Am Rev Respir Dis*1987;135:1271.

55. **Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP.** Airway inflammation in young marijuana and tobacco smokers. *Am J. Respir Crit Care Med* 1998;157:928-937.

56. **Fleisher M, Winawer S J, and Zauber A G.** Aspergillosis and marijuana. *Annals of Internal Medicine.* 1991;115:578-579.

57. **Ramirez R J.** Acute pulmonary histoplasmosis: newly recognized hazard of marijuana plant hunters. *American Journal of Medicine.* 1990; 88: 5-60N-5-62N.

58. **Taylor D N, et al.** Salmonellosis associated with marijuana: a multistate outbreak traced by plasmid fingerprinting. *NEJM.* 1982;306:1249-1254.

59. **Fried P A,** Marijuana use by pregnant women: Neurobehavioral effects in neonates. *Drug and Alcohol Dependence.* 1980 6:415-424.

60. **Fried P A, Watkinson B, and Willan.** Marijuana use during pregnancy and decreased length of Gestation. *American Journal of Obstet. Gynecol.* 1984;150:23-27.

61. **Hingson R, et al.** Effects of maternal drinking and marijuana use on fetal growth and development. *Pediatrics.* 1982;70:539-546.

62. **Kline J, Stein Z, Hutzler J.** Cigarettes, alcohol, and marijuana: varying associations with birthweight. *International Journal of Epidemiology.* 1987;16:44-51.

63. **Zimmerman S, Zimmerman A M.** Genetic effects of marijuana. *The International Journal of Addictions.* 1990-1991;25:19-23.

64. **Zuckerman B, et. al.** Effects of maternal marijuana and cocaine use on fetal growth.*NEJM.* 1989;320:762-768.

65. **Barnett G, Chiang C N.** Effects of marijuana on testosterone in male subjects. *J. Theor Biol.* 1983;104:685-692.

66. **Mendelson J H, et al.** Marijuana smoking suppresses leuteinizing hormone in women. *Journal of Pharm. Exp. Therapeutics.* 1986;237:862-866.

67. **Kolodny R C, et al.** Depression of plasma testosterone with acute marijuana administration. *The Pharmacology of Marijuana,* Raven Press, New York.1976;217:225.

68. **Mendelson J H, Mello N K, and Ellingvoe J.** Acute effects of marijuana smoking on prolactin levels in human females. *The Journal of Pharm. and Exp. Therap.* 1985;232::220-222.

69. **Mueller B A, Daling J R, Weiss N S, and Moore D R.** Recreational drug use and the risk of primary infertility. *Epidemiology.* 1990; 1:195-200.

70. **Day NL, et al.** Effect of Prenatal Marijuana Exposure on the Cognitive Development of Offspring at Age Three. *Neurotoxicology and Teratology*1994;16:169-175.

71. **Dahl RE, et al.** A Longitudinal Study of Prenatal Marijuana Use. *Archives of Pediatric and Adolescent Medicine.* 1995;149:145-50.

72. **Fried PA,** The Ottawa Prenatal Prospective Study: Methodological Issues and Findings *Life Sciences, 1995;*56:2159-2168.

73. **Cabral G A, Vasquez R.** Delta-9-Tetrahydrocannabinol suppresses macrophage extrinsic anti-herpesvirus activity. *Cannabis: Physiopathology, Epidemiology, Detection.* CRC Press1993:137-153.

74. **Gross G, Roussaki A,** Ikenberg, Drees N. Genital warts do not respond to systemic recombinant interferon alfa-2 treatment during cannabis consumption. *Dermatologica* 1991; 183:203-207.

75. **Daaka Y, Zhu W, Friedman H, Klein T W.** Induction of Interleukin-2 alpha gene by delta-9-THC is mediated by nuclear factor *k*B and CBa cannabinoid receptor. *DNA and Cell Biology* 1997;16:301-309.

76. **Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI.** Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561-564.

77. **Munro S, Thomas KL, Abu-Shaar M.** Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365:61-65.

78. **Martin WJ.** Basic Mechanisms of Cannabinoid-induced analgesia. Technical corner, International Association for the Study of Pain. 1999 http://www.iasp-pain.org/TC99Summer.html.

79. **Voth EA,** Guidelines for prescribing medical marijuana West J Med2001;175:305-306. West J Med 2001;175:305-306 http://www.ewjm.com/cgi/content/full/175/5/305.

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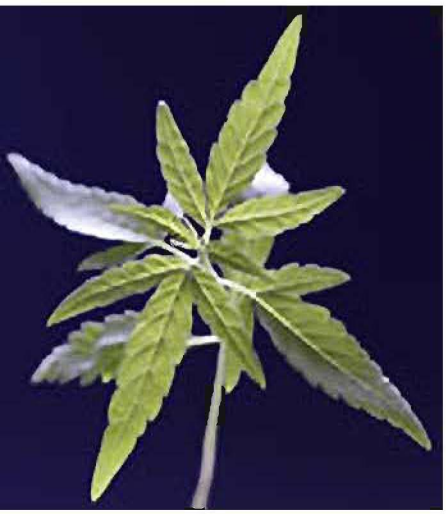

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Edited by Eric A. Voth, MD, FACP, and David A. Gross, MD, FAAP, our intended readership includes clinicians, clinical researchers, policymakers, prevention specialists and the interested public.

IN THIS ISSUE

THE JOURNAL OF
GLOBAL DRUG POLICY AND PRACTICE

From Mockery to Medicine: The Story of the Development of a Serious Modern Medicine

Andrea G. Barthwell, MD, FASAM

Introduction

In the United States, the effort to legalize cannabis for use as "medical marijuana" has focused on making it available to people as a home remedy, or perhaps an herbal treatment akin to a dietary supplement, but not as a Food and Drug Administration (FDA) - approved medicine. To obtain such approval, a therapeutic product must be quality-controlled in all aspects of manufacture, standardized by composition and dose, tested in preclinical and clinical studies, and administered by means of an appropriate delivery system or dosage form. It must, in short, meet the rigorous standards for quality, safety and efficacy that have been laid down by regulatory authorities. Crude herbal cannabis could never pass the FDA's rigorous standards.

The FDA recognizes that under appropriately controlled conditions, modern research and technologies enable complex botanical materials to be developed into pharmaceuticals in accordance with both scientific and regulatory rigor. The agency has issued a guidance document for these circumstances, acknowledging that complex composition is not inherently problematic.[1] Rather, as with all pharmaceutical products, the important factors are the application of quality control processes at each stage in the manufacturing process; characterization, specification, and standardization of the components; and the completion of appropriate preclinical and clinical studies—in other words; proof of quality, safety, and efficacy.

Crude herbal cannabis varies significantly in composition and consistency, depending on which strain is being propagated and under what conditions it is cultivated, harvested, stored, and prepared. Persons using crude herbal cannabis use materials that vary in quality and content. These materials may be contaminated with harmful pesticides, fungi, or heavy metals. Such contaminants have the potential to pose a threat to both seriously ill and healthy people. There is at least one report of death from a rare neurological condition, which may have occurred as a complication of an allergic reaction to pesticide-laden cannabis handled at the dispensary .[2]

Evidence-Based Medicine

Crude cannabis and the methods used to deliver it to patients have not met the minimum standards required of legitimate medicines and, therefore, do not belong in our system of modern medical practice. Modern medical practice is evidence-based. In advising patients, physicians rely in large part upon the results of controlled clinical trials conducted in accordance with established scientific principles. Preclinical studies and early (Phase 1) clinical trials demonstrate whether the product is likely to be harmful to humans. Randomized, double blind, placebo-controlled clinical trials (Phases 2 and 3 clinical trials)—the "gold standard" of scientific research—provide information about a medical product's safety and efficacy that usually accurately predicts real world expectations for a new medication.

GW Pharmaceuticals' Development Program

GW Pharmaceuticals (GW) has embarked on a full pharmaceutical development program for cannabinoids that pursues both scientific and regulatory rigor, making it the first company in the world to produce a complex, heterogeneous pharmaceutical product derived from the cannabis plant. As GW's research has shown [3,4,5], the process of developing botanically derived cannabinoid medicines is a challenging one, necessitating standardized raw materials and innovative extraction methods for the non-water soluble active ingredients.

Moreover, GW has rigorously adhered to the high principles of science and evidence-based medicine in its development program, having already conducted eight Phase 3 clinical trials and numerous smaller Phase 1 and Phase 2 studies with more than 2,000 patients participating. These clinical studies have investigated the use of Sativex® in the treatment of symptoms of multiple sclerosis, including spasticity [6], bladder dysfunction [7], tremor, spasm, sleep disturbance, pain [8,9], neuropathic pain of various origins—such as spinal cord injury, diabetic neuropathy, MS, brachial plexus avulsion—[10,11,12], rheumatoid arthritis [13], and cancer pain [14].

Using the latest technology, GW produces highly standardized cannabis "chemovars"—plant strains characterized by their chemical composition—that serve as the starting materials for its pharmaceutical development process. Computer-controlled glasshouses rigorously monitor and control growing conditions. Sensors automatically adjust light exposure to respond to changes in length and quality of daylight. Organic growing medium and specific quality control techniques ensure that no pesticides, heavy metals or microbiological contaminants are present. Botanists employ sophisticated breeding techniques

to create unique chemovars that express specific cannabinoid ratios. Clonal reproduction maintains cannabinoid ratios and chemical composition throughout subsequent generations.

GW cultivates two primary cloned lines not normally found in nature, one in which cannabidiol (CBD), a non-psychoactive cannabinoid, is predominant. CBD is believed to significantly attenuate delta-9-tetrahydrocannabinol (Delta-9-THC) - associated side effects, such as intoxication and tachycardia [15](6). This CBD clonal line and a predominantly Delta-9-THC plant strain were developed through applied Mendelian genetics and are proprietary to GW.

Manufacture and Formulation Considerations

Cannabinoids are not water-soluble; therefore, studies are required to identify excipients that will permit the formulation of cannabinoids into finished pharmaceutical products. Cannabinoids, particularly Delta-9-THC, are also very unstable; therefore, research is required again to select formulations and to structure the manufacturing and storage processes to ensure that the medicines will maintain an appropriate shelf life. A small change in formulation can have substantial effects on both bioavailability and stability. GW has conducted numerous trials to ascertain the optimal formulation for its lead product, Sativex®, which contains a specific proportion of cannabinoids with ethanol and propylene glycol excipients.

Once crude cannabis plant material is standardized, as is achieved in the manufacture of Sativex®, it is only the first step in producing a modern medicine. A cannabis-based medicine must be fully researched and strictly regulated at every step in its manufacturing cycle; therefore, the subsequent steps of the manufacturing process—from harvesting to drying to the various steps of extraction and formulation—are also standardized and subject to stringent quality control testing procedures. GW blends the extracts from the two clonal lines to produce Sativex®, a ratio of 1.08:1 of Delta-9-THC and CBD. The final product is highly characterized, and tight specifications are set for all the significant cannabinoids and other components, such as terpenes, plant waxes, and flavonoids. These are common plant components present in many food and flavoring items.

Delivery System Considerations

Once standardized in composition, a cannabinoid medication must be administered in a manner that enables a patient to obtain a reliable dose with predictable effect. It is especially important to allow the patient to adjust his or her dose in order to obtain relief of symptoms while minimizing side effects, particularly disabling psychoactivity. It is also essential that the delivery system does not expose the user to harmful impurities, such as pyrolytic products.

There is no proven safe and reliable delivery system for crude herbal cannabis. If crude cannabis is smoked, it exposes seriously ill patients to dangerous pyrolytic products. If it is eaten in baked goods, ground and packaged in gel caps, or consumed as tea, the intestinal absorption is very erratic from day to day or even throughout one day, and hence its effect, including its psychoactive effect, is quite variable and unpredictable. It is also subject to first-pass metabolism to metabolites with more psychoactivity than the parent compound. In such delivery methods the dose and composition are uncertain.

Pulmonary Delivery Carries Associated Risks and Harms

Tests of the crude cannabis plant in all studies to date show that burn-and-inhale administration is simply a toxic alternative delivery system for high doses of Delta-9-THC. Given that oral Delta-9-THC is available as a Schedule 3 prescription drug, one might argue that there should be no need for smoked crude marijuana. The individuals who prefer the smoked, home remedy approach say they do so because smoking marijuana gives them the ability to titrate their dose or control rate of onset of action. The formulation issue is a valid one in clinical medicine that needs to be addressed and has been done so by GW such that patients can achieve a therapeutic effect with significantly reduced risk of psychoactive effects.

Vaporization, a popular trend among cannabis smokers, does not resolve these issues. A recent study showed that when herbal cannabis is vaporized, several harmful carcinogens (polyaromatic hydrocarbons) —while reduced—were still delivered to the lungs[16] . Furthermore, currently available vaporizers do not provide the precise standardization of dose necessary for a prescription medicine. In addition, when patients inhale cannabis (whether smoked or vaporized), their Delta-9-THC blood levels rise rapidly to high levels, making it probable that many of them will not be able to control psychoactive side effects. Rapid increases in Delta-9-THC blood levels are also associated with greater tendency to intoxication and dependence.

Unique Delivery System Developed

Because Delta-9-THC is psychoactive, it is essential that a Delta-9-THC-containing product be delivered in a manner that enables a patient to remain within the “therapeutic window,” i.e., predictably to obtain symptom relief without experiencing untoward central nervous system side effects. Seriously ill patients with debilitating chronic disorders do not wish to "trade one disability for another" to be intoxicated; they want to work, care for their families, and be productive. Accordingly, the delivery system must not only provide standardized doses but must also enable the physician and patient to manage the dosing increments. The regulated system of medicine offers the only hope in the area of formulation to safely address the delivery system needs of patients.

To address this issue, GW Pharmaceuticals pioneered the development of an oromucosal spray for the delivery of Sativex®. Its onset of action is 15-40 minutes, which is rapid enough to enable chronically ill patients to titrate their dose, but not so rapid as to be rewarding for its euphoriant effects. The oromucosal spray contains exactly 100 micro liters of Sativex® (2.7 mg. of Delta-9-THC and 2.5 mg. of CBD)[17]. GW has monitored "intoxication scores" of its patients, and the level of intoxication among patients (who are receiving relief of symptoms) is essentially no higher than placebo [9]. It is, therefore, clearly not the case that patients achieve symptom relief only at the cost of intoxication. Furthermore, many patients have been taking Sativex® for one to four years and have not escalated their dose during that time [6 18]. Although evidence suggests that illicit users may become tolerant to the psychoactive effects of cannabis and must increase their use, patients using Sativex® do not develop tolerance to its therapeutic benefits.

Additionally, a group of MS patients on Sativex® for one year or more voluntarily stopped Sativex® administration abruptly. While symptom re-emergence occurred within seven to 10 days for most, none had significant withdrawal symptoms [18], and all who resumed the medicine regained symptomatic control at previously established doses. It is common to see symptom re-emergence after adequate control when medications are abruptly discontinued, sometimes paired with withdrawal.

This intermediate-onset delivery system, which also permits patients to take small increments of medicine, is believed to be an improvement over other forms of administration, particularly oral administration. Gastrointestinal absorption of oral Delta-9-THC exposes the compound to a first pass effect and hepatic metabolism of Delta-9-THC to 11-hydroxy-THC, thought to be more psychoactive than Delta-9-THC with an onset of effect that is long and unpredictable. Patients, therefore, cannot reliably titrate their dose after oral administration to avoid side effects, including psychoactivity. As the Institute of Medicine has stated [19].

> 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 plasma concentrations are not attained until two to four hours after dosing…
> Variation in individual response is highest for oral Delta-9-THC and bioavailability is lowest.

Abuse Liability Varies with Rate of Change of Blood Level Over Time

Inhaled Delta-9-THC is neither an optimal nor desirable delivery system for most patients. When Delta-9-THC is inhaled (as in smoking or vaporizing cannabis), Delta-9-THC blood levels rise to high levels quickly, with the resulting rise in blood level over a short period of time associated with greater tendency to intoxication and dependence. In a Phase 1 study, using a predominantly-Delta-9-THC extract delivered by means of a high technology vaporizer, GW found that concomitantly high intoxication levels accompanied such a rapid Delta-9-THC blood level rise [17]. A similarly high rise in Delta-9-THC blood levels was demonstrated in a recent Phase 1 trial that tested an inhaled version of dronabinol; therefore, it is likely that many patients who inhale Delta-9-THC will have a difficult time controlling intoxication and remaining within the therapeutic window [20]. Most patients with chronic conditions do not need an immediate onset product, particularly when there is such an undesirable tradeoff of symptom relief vs. intoxication. Sativex's® onset of action of 15-40 minutes provides sufficiently rapid symptom relief for such conditions, especially as patients learn over time to adjust their small doses to stabilize and maintain therapeutic blood levels.

The Scheduling of Cannabinoid-Containing Products under the Controlled Substances Act

Under the federal Controlled Substances Act (CSA), both cannabis and Delta-9-THC are Schedule I substances. If a cannabis-derived product like Sativex® were successful in obtaining FDA marketing approval, that specific product would need to be transferred out of Schedule I to another schedule, since FDA approval demonstrates that the product has "an accepted medical use in the US." This would not, however, necessitate a rescheduling of either herbal cannabis or Delta-9-THC. For example, Marinol® is located in Schedule III, while Delta-9-THC remains in Schedule I. Moreover, even if cannabis and Delta-9-THC (as active ingredients) were moved to Schedule II, that would not mean that crude herbal cannabis, or any cannabis or Delta-9-THC preparation, would become immediately available to patients by prescription. Rather, each and every medical product in interstate commerce must have gone through the FDA process on its own merits and must have satisfied FDA's intense scrutiny before physicians may prescribe and pharmacists may dispense it. Opium and coca leaves are in Schedule II, but crude opium or coca products are not distributed to patients. The entire "rescheduling of cannabis" argument made by cannabis advocates demonstrates a profound misunderstanding of the process by which serious prescription medicines become available to patients in the US.

Conclusion

Sativex® is a pharmaceutical product standardized in composition, formulation, and dose, which is administered by means of an appropriate delivery system, and which has been—and continues to be—tested in properly controlled preclinical and clinical studies. It is not crude cannabis, which is none of those things. Acceptance of Sativex ® [and its proof of efficacy] for specific indications does not suggest the acceptance of crude cannabis or prove its medical usefulness for the reasons set forth and many others. All medicinal products must be subjected to, and satisfy, the FDA's rigorous scrutiny before becoming available to patients in need. GW has consistently maintained that crude herbal cannabis can never meet

the regulatory standards of the FDA and those of regulatory bodies in most other countries around the world [21] . These standards are mandatory if the modern medical model—informed patients working with and being advised by knowledgeable physicians to identify appropriate treatment options—is ever to be attained with a cannabis-based medicine.

It is not surprising that the concept of "medical marijuana" has been foisted on a largely unwilling and disapproving medical profession by legislative and ballot initiatives. Physicians who want medicines to meet the tests of quality, safety, and efficacy are not its proponents. Rather, the primary supporters are those whose ultimate agenda is to legalize marijuana for non-medical purposes. For the safety of patients and the security of physicians, physicians must draw a bright line between approved, legitimate medications and drugs of abuse that are used for the purpose of obtaining a euphoric "high." Physicians must insist that the medicinal products they recommend to patients be subjected to, and satisfy, the FDA's rigorous scrutiny.

1. **Food and Drug Administration.** Guidance for industry: Botanical drug products. In: Services UDoHaH, editor.: US Government; 2004. p. 48.

2. **Gardner F. Jane Weirick**: death of an organizer. Counterpunch.Oct. 29, 2005 http://www.counterpunch.org/gardner10292005.html (accessed March 25, 2006)

3. **Potter D. Growth and morphology of medicinal cannabis**. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 17-54.

4. **DeMeijer E.** The breeding of Cannabis cultivars for pharmaceutical end uses. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 55-69.

5. **Whittle B., Guy G.** Development of cannabis-based medicines: risk, benefit and serendipity. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 427-466.

6. **Collin C.** A cannabis-based medicine (Sativex) has sustained efficacy in the treatment of spasticity in multiple sclerosis. Association of British Neurologists; 2005 April 1; Belfast, Northern Ireland; 2005.

7. **Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ.** An open-label pilot study of cannabis based extracts for bladder dysfunction in advanced multiple sclerosis. Multiple Sclerosis. 2004;10:425-33.

8. **Wade DT, Makela P, Robson P, House H, Bateman C.** 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. Mult Scler. 2004 Aug;10(4):434-41.

9. **Wade DT, Robson P, House H, Makela P, Aram J.** A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clinical Rehabilitation. 2003;17:18-26.

10. **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 Dec;112(3):299-306.

11. **Notcutt W.** Cannabis in the treatment of chronic pain. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 271-300.

12. **Rog DJ, Nurmiko T, Friede T, Young C.** Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. Neurology. 2005;65(6):812-9.

13. **Blake DR, Robson P, Ho M, Jubb RW, McCabe CS.** Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006 Jan;45(1):50-2.

14. **Johnson JR, Potts R.** Cannabis-based medicines in the treatment of cancer pain: a randomised, double-blind, parallel group, placebo controlled, comparative study of the efficacy, safety and tolerability of Sativex and Tetranabinex in patients with cancer-related pain. British Pain Society; 2005 March 8-11; Edinburgh, Scotland; 2005.

15. **Ashton, CH, Moore, PB, Gallagher, P, Young, AH,** Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential. Journal of Psychopharmacology. 2005; 19(3):293-300.

16. **Gieringer D, St. Laurent J, Goodrich S.** Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. Journal of Cannabis Therapeutics. 2004;4(1):7-27.

17. **Robson P, Guy GW.** Clinical studies of cannabis-based medicine. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 229-70.

18. Canada has approved Sativex® for the treatment of neuropathic pain in multiple sclerosis. GW is currently preparing additional European regulatory submissions for other medical indications. The UK has authorized Sativex® to be prescribed on a named patient basis to patients whose physicians believe they may benefit from the product. Additionally, the Catalonian government in Spain has permitted it to be prescribed on a compassionate basis. On January 3, 2006, GW announced that the FDA had agreed to permit Sativex® to proceed to Phase III clinical trials, the final stage of research that a product must undergo before it is submitted for marketing approval. GW will test Sativex® in patients with advanced cancer, whose pain is not being adequately controlled with opiates. The trials will commence in the latter part of 2006 and a marketing application should be submitted 24-36 months after the trials begin. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Multiple Sclerosis. 2006;(in press).

19. **Joy JE, Watson SJ, Benson JA, Jr.** Marijuana and medicine: Assessing the science base. Washington, DC: Institute of Medicine; 1999; p. 203.

20. **Miller J, Meuwsen I, ZumBrunnen T, de Vries M.** A Phase I evaluation of pulmonary dronabinol administered via a pressurized metered dose inhaler in healthy volunteers. American Academy of Neurology; 2005 April 14; Miami Beach, FL; 2005.

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I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled except for the following:

Consultant, GW Pharmaceuticals

Author: Andrea G. Barthwell, MD
Date: July 17, 2006

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Marijuana and Adolescents

Edward A. Jacobs, MD, FAAP

Introduction

Marijuana is the most common illicit drug used by youth in the United States [1]. There is an increasing body of scientific evidence showing the short term and long term consequences of its use. These consequences are often made more serious because preadolescents and adolescents have not completed their physical, emotional, or social development. Anything that could interfere significantly with that development has the potential for a greater impact than the consequences of similar use by a fully mature and developed adult. This has major implications for the individual teen, his/her family, the school, the community, and the health care professionals whose responsibility it is to care for them. For health care providers, this is true regardless of whether one is a primary care provider, specialist, subspecialist, emergency room provider, or mental health or addiction specialist.

Epidemiology and Patterns of Use

Although the use of marijuana by youth has been trending downward over the past few years, it still remains unacceptably high [1]. In 2005, the "Monitoring the Future" study of almost 50,000 students in 400 schools showed that the lifetime prevalence of marijuana use for 8th, 10th, and 12th graders was 16.5%, 34.1%, and 44.8%. The annual prevalence of use was 12.2%, 26.6%, and 33.6%, and the 30-day prevalence of use for each grade was 6.6%, 15.2%, and 19.8%. The most alarming aspects of these numbers are that approximately 1 in 9 eighth-graders and approximately 1 in 4 tenth-graders are using marijuana once or more per year, that in all categories the use doubles between the 8th and 10th grades, and almost 20% of our high school seniors are using marijuana 1 or more times per month. Furthermore, various studies have cited the age of first use as averaging approximately 13-14 years of age, which means many have started using prior to that age [2,3,4].

Risk and Protective Factors

There are several risk factors which affect the decision to use marijuana by adolescents and preadolescents. These include peer pressure, low self-esteem, history of family use and attitudes toward drug use, isolation, depression and other psychological issues, school failure, and availability of the drug [3,5,11,12]. In fact, drug use has often been referred to as an "infectious disease" because you get it from the people around you. Although school failure, low self-esteem, and emotional disturbance are often cited as risk factors for the use of marijuana and other drugs, the long interval between onset of use and the appearance of significant clinical symptoms including school failure, emotional lability, and more overt psychological and psychiatric symptoms makes it essential to recognize that quite often it is the repeated marijuana use producing these observed behaviors rather than the preexisting behaviors causing the initiation of marijuana use.

One of the most important risk factors for marijuana use by teenagers is their perception of risk to themselves by smoking marijuana [1]. The perceived risk can be any combination of physical, social, or punitive consequences. This particular factor has been tracked by the "Monitoring the Future" study for many years and shows a clear inverse relationship between use and perception of "great risk" in using regularly [1](figure 1). In the 1970s, when little was known of the risks of use and youth perception of self-risk was almost nonexistent, use was rampant. In the 1980s and very early 1990s when teens' perception of risk increased significantly secondary to increased scientific evidence of harm with repeated use, coupled with a combined effort by parents, schools, community, and government; the use of marijuana by teens steadily decreased. Starting in the early to mid-1990s, the perception of risk with using marijuana began to decrease, and marijuana use by youth began to increase again to a peak in the late 1990s. Over the past 5 years, the cycle has again begun to reverse, and use has trended downward. The reasons for this latest downward trend are not fully understood. However, the observation that it has not decreased as significantly as in the 1980s is felt by many to be due in part to the fact that the national and local debate over marijuana as a "medicine" and its legalization has not been lost on our young people's perception of diminished risk with using [22].

Conversely, protective factors which mitigate against use of marijuana by adolescents include strong family relationships, responsible role models, high academic expectations by both the teen and his/her parents, involvement in extracurricular activities, sober peers, close parental supervision, and religious faith [3,4,6,12].

Adolescent Development

Adolescence is synonymous with change. It is the period of one's life when an individual changes physiologically, emotionally, socially, and academically from a child in a protected environment to an independently functioning adult. It is a time to learn how to deal with success and failure, praise and rejection, happiness and disappointment, frustration and confrontation. It is a time to make choices and deal with the consequences of those choices while still in a semi-controlled and semi-protected environment. Traditionally, this time frame was believed to start at approximately 12 years of age and to be completed by 18 years of age. In the past several years, there has been considerable discussion that this time frame has broadened, with the onset beginning at 8-10 years of age and extending into one's 20s, especially for the emotional and social developmental components.

Thus, any substance which, with repeated use, impacts or negatively interferes with this developmental trajectory is very serious cause for concern. If one turns to the use of marijuana to avoid or blunt the negative experiences or to try to enhance the positive experiences of adolescence, he/she never learns these lessons and the coping mechanisms

necessary to successfully manage them [17,18]. He/she emerges from this critical developmental period as an "adult adolescent." Furthermore, it is extremely difficult, and for many it is impossible, to go back as an adult and relearn those crucial lessons and skills.

Consequences of Use

Marijuana is not an innocuous drug, and adolescents are not fully mature adults. Effects which are minimal or undetectable in mature adults may have an increased or different impact on an adolescent. Also, effects which might manifest over long periods of time and with repeated use, such as genetic and reproductive effects and cancer-associated effects, may only appear many years later.

Repeated marijuana use has been associated with significant adverse effects on many organ systems [2,4,5,7,18]. The extent to which this impact occurs depends on factors such as potency of delta-9 THC in each use, the method of consumption, the chronicity of use, the effects of the over 400 non-delta 9 THC chemicals found in the crude marijuana plant, and the presence of adulterating substances.

The issue of potency of the delta-9 THC in marijuana is extremely important and deserves special mention [2,18]. Improved technology has resulted in the production of much more potent marijuana over the past 25 years. In the 1970s, the average potency of marijuana was less than 1% THC. By the late 1990s, the average was 3.5-4% THC with some varieties, such as sinsemilla, being between 6-10% or more. The impact of recurrent use of this much more potent marijuana on adolescent users can be very significant and very worrisome.

Acute Effects [2,3,4,5,18,23]

The acute effects of marijuana intoxication may last as long as 12 to 24 hours after use and can be divided into the rapid uptake, or accumulation, phase and the slow release elimination phase. The onset of the rapid uptake phase during which the delta-9 THC is entering the brain during active use may begin within 15 to 30 minutes after initiation of use. Its effects include euphoria, conjunctival injection, elevated blood pressure, tachycardia, tachypnea, initial bronchial dilatation followed later by bronchial constriction, and decreased intraocular pressure. This phase usually lasts 1 to 3 hours after cessation of use. It is then followed by a slow release elimination phase during which the delta-9 THC is slowly released from the fatty tissue of the brain and other organs. In this elimination phase, which can last 12 to 24 hours after use, effects include drowsiness, calmness, increased appetite, irritation and dryness of the nose and throat, hypotonia, tremors, and, most importantly, impaired reaction time.
These effects are transient and usually not deleterious to an otherwise healthy adolescent. However, if the teen has known or undiagnosed underlying medical, psychological, or psychiatric problems, these acute effects can be of significant consequence and can occur or persist for hours after the euphoria has subsided. In addition, these effects are dose-related and affected by both potency and frequency of use. When marijuana is used in moderate to large doses, patients may have significantly impaired motor function and reduced reaction times, decreased speech fluency, impaired short term memory, inability to perform complex tasks, acute panic attacks, anxiety attacks, psychotic episodes, hallucinations, and delusions. These effects can be difficult to distinguish from many psychiatric disturbances. In addition, through its effects on coordination, cognition, reaction time, and decision-making, marijuana use contributes to injuries and accidental deaths in adolescents, especially in motor vehicle accidents. Plus, its effects on judgment and decision making often contribute to an increase in other risk-taking behaviors such as unprotected sexual activity, unintended teen pregnancy, and other drug use.

Chronic Effects [2,3,4,5,18,23]

Delta-9 THC is very lipophilic, and repeated use of marijuana results in accumulation of delta-9 THC in the brain and other fatty tissues of the body. Because it is slowly released from these adipose tissue sites, a reservoir of cannabinoids exists which is replenished with repeated use. In fact, with a use pattern of 1 to 2 times per week or more, the reservoir is constantly renewed, and it will take 4 to 6 weeks or often longer to dissipate once use has completely stopped. Thus, repeated marijuana use impacts the brain, the lungs, the cardiovascular system, the immune system, the endocrine system and puberty, and pregnancy and the fetus and newborn.

The impact of repeated marijuana use on brain function resulting in behavioral and cognitive effects is well known, and the consequences on the not-yet-fully mature brain of the adolescent are even more concerning. While there are varying results of studies of chronic marijuana use and permanent cognitive dysfunction in adults who have stopped using one or more years prior to participation in these studies, there is no disagreement about the significant negative effects on learning, short term memory, and attention span of adolescents who are under the influence of frequent/repeated marijuana use. In addition, a syndrome known by the terms "amotivational syndrome" or "chronic cannabis syndrome" has been reported in chronic heavy marijuana users. This syndrome has been characterized by cognitive impairment, the inability to sustain attention, and a reduced ability to establish or maintain goal-directed thinking and behaviors, resulting in underachievement in the attainment of jobs that require less challenge and technical acuity. In adolescents, this can manifest as an A or B student being content with merely passing grades or dropping out of or not caring about extracurricular activities with which the teen was previously very involved.

Furthermore, there is increasing evidence that marijuana use increases the risk of developing schizophrenia, anxiety, and depression. However, it is as yet unclear whether marijuana actually causes psychiatric illness in individuals who would not otherwise be predisposed, or whether it simply triggers the onset of conditions in those who have a genetic or other predisposition.

Recurrent and chronic smoking of marijuana results in an increased risk of development of chronic lung disease. This increased risk is a result of several factors compared to tobacco smoking. First, the method of inhalation delivers almost twice as much smoke as from a tobacco cigarette. Second, the depth of inspiration and breath holding time is significantly longer with marijuana. Third, marijuana joints have no filter and deliver 50% more carcinogens and 400% more tars and

increase blood carboxyhemaglobin by up to five-fold. The increased mucus production, irritation, and bronchospasm produced by recurrent use may thus result in increased chronic and recurrent respiratory symptoms. The relationship of chronic marijuana smoking to respiratory tract concerns including lung cancer has not been fully determined. In light of what is known about tobacco, it is fair to assume that adolescent chronic marijuana smokers are probably at increased risk, especially since they are starting at such an early age. In addition, the theoretical potential increased risk for oral and nasopharyngeal cancers is currently unknown.
Immunologic function may be affected by repeated and chronic marijuana use. Components of marijuana influence the immune system and affect the anti-tumor activities of the body. Marijuana receptors have been found in T and B lymphocytes and macrophages, suggesting an ability for immunosuppression by delta-9 THC. Although increased rates of infection have not been reported among marijuana users, the incremental impact on patients with recurrent respiratory infection cannot be discounted.
Puberty represents a particularly vulnerable period for an adolescent, and recurrent marijuana use may be especially dangerous during this time. Chronic use has been reported to be associated with decreased sperm mobility, decreased sperm counts, decreased circulating testosterone levels, decreased libido, gynecomastia in males, and irregular ovulation, irregular menses, and galactorrhea in females, as well as decreased pituitary gonadotropin levels. Although the exact implications and long-term consequences of the findings are not completely understood, anything that may affect or interfere with the orderly pubertal development and sexual reproductive function is very troubling.

Marijuana is also the most commonly used illicit substance during pregnancy, and teen pregnancy is a significant societal problem. Infants born to mothers who smoked marijuana during pregnancy have significantly smaller lengths, weights, and head circumferences. In addition, metabolites of marijuana cross the placenta and are also found in breast milk. One study of toddlers who were exposed to prenatal marijuana showed alterations in the language skills of those toddlers and, by four years of age, showed pronounced differences in memory and verbal ability. Although the implications of these findings await further study, anything that can impact the brain during the most rapidly developing period of one's life is cause for very serious concern.
Finally, marijuana use by youth cannot be considered in isolation. While some adolescents will use once or infrequently and stop and some will continue with repeated use but not with other substances, a significant proportion of adolescents will use marijuana as a "gateway" or precursor to the use of other drugs. The reasons for this are multifactoral and include the seeking of a more intense or sustaining mind-altering experience, the relationship of marijuana use with other risk-taking behaviors, the alteration of judgment with repeated use and while under the influence, and the association with drug -using peers. Although the use of marijuana does not necessarily predict progression to the use of additional drugs, one study showed that adolescents who use marijuana are 104 times more likely to use cocaine than are teens who never used marijuana.

Diagnosis

The signs and symptoms of acute intoxication and recurrent and chronic marijuana use have been discussed above. It is important to note that these signs and symptoms often overlap with the signs and symptoms of other drugs of abuse including alcohol use. For an adolescent, the most important aspect of initial diagnosis is not so much which drug is being used but the recognition that the adolescent is in fact using. Often there is more than one drug involved by the time the teen's symptoms become recognized as a result of drug use.

There are many excellent publications on the principles and elements of evaluating adolescents for substance abuse, and a detailed discussion of this area is beyond the scope of this publication [3,4,7,8,13,16,19]. However, a few general comments are noteworthy. When dealing with adolescents, it is most often successful to gather the information in a nonjudgmental fashion and become more focused as the history-gathering process proceeds. However, once the information has been obtained, it is certainly appropriate as a health care provider to give an opinion or judgment on the adolescent's health and behavior and the consequences of continued use. Do not forget to acknowledge and compliment the non-user on his/her decision to not use.
Because many health care providers and others feel uncomfortable or less skilled in interviewing teens, especially in this sensitive area, the use of screening questionnaires has become popular. One such brief office instrument is the CRAFFT questionnaire which has been validated and field tested [19]. It consists of six questions with any two or more positive answers being an indication for a more comprehensive assessment or referral for such.

Another area of diagnostic importance is the nontraditional presentations of adolescent marijuana use. These are especially important for those specialists, subspecialists, and emergency room physicians who might not have the experience or comfort with adolescents who are using marijuana and other drugs. Examples of some of these presentations include the adolescent who presents with such symptoms as recurrent fatigue, headaches, weight loss, abdominal pain, lethargy, school absenteeism, symptoms of ADD appearing after age 11 or 12, depression, or other psychological symptoms, such as anxiety or panic attacks. Other more common nontraditional presentations include symptoms of chronic or recurrent mononucleosis syndrome in spite of negative laboratory studies and chronic or recurrent asthma, bronchitis, sinusitis, pharyngitis, and particularly uvulitis, especially when unresponsive to conventional treatment or to treatment that has been successful in the past. One should also consider marijuana use in the evaluation of trauma, especially recurrent trauma, and trauma involving motor vehicle accidents, including bicycles, skateboards, and scooters. Lastly, one must always be aware that an adolescent's symptoms may not be the result of that teen's use of marijuana or other drugs, but is presenting as the index case and may be the result of another sibling's or family member's use with the resultant chaos and turmoil within the family [7,12]. This is frequently the situation when a younger sibling presents with nonspecific and functional symptoms, such as recurrent abdominal pain, headaches, depression, sleep disorders, or escalating out-of-control behavior.

Laboratory

Once the diagnosis of marijuana use is suspected or confirmed by history, the next consideration is the role of the laboratory, or more specifically, urine testing. In general, the role of the laboratory in the evaluation of marijuana use is the

same as its role in the evaluation of all other medical conditions. First, it can be used to confirm information obtained from the history and/or physical examination. Second, it can be used to help explain signs or symptoms which cannot be clearly explained from the history or physical exam. Thirdly, it can be used to assess abstinence as a component of a treatment program.

Initially, a positive clinical history for marijuana use may obviate the need for further laboratory testing, unless there is suspicion of the concomitant use of other drugs. Although hair, blood, saliva, stool, and meconium may be used for testing, urine is the most commonly tested body fluid for marijuana.

In considering the use of urine testing in the evaluation of marijuana use, there are several critical factors of which one must be aware in order to correctly interpret the results. There are several excellent in-depth discussions of these issues including an American Academy of Pediatrics policy statement with an addendum/update soon to be published (personal communication), but some items deserve special consideration [3,4,9,15]. First is the issue of consent and confidentiality. Except for situations such as the inability of the patient to provide consent by virtue of age, maturity, or impaired mental status or judgment, urine testing should be done with the consent of the patient, and with assurances of confidentiality whenever possible [14]. Second, the source of the specimen must be known and procedures to insure that contamination, dilution, substitution, or other acts, whether purposeful or accidental, intended to alter the specimen do not occur. Third, knowledge of the pharmaco-kinetics and elimination profile of marijuana and of the temporal relationships of frequency of use and time of last use to the time of obtaining the specimen is important. Fourth, it is necessary to know the capability of the particular laboratory to identify marijuana and its metabolites, as well as which tests it uses and the sensitivity and specificity of these tests. This is especially important because most laboratories use a cutoff level of 50 or 100 nanograms. If the actual amount of marijuana metabolites is below that amount, the laboratory will report as "none detected," resulting in a false negative from a clinical standpoint. Fifth, awareness of all of the factors which might result in a false positive or false negative result is essential to the correct interpretation of the results. Lastly, all positives must be confirmed by the more precise gas chromatography/mass spectrometry (GC/MS) technology.

While most health care professionals can agree on the use of urine testing in the evaluation and management of the individual adolescent, there is currently significant debate about the use of laboratory testing as a component of a comprehensive program to prevent adolescents from using marijuana and other drugs. Much of this discussion centers around the distinction between the terms "screening" and "testing" for marijuana and other drugs of abuse. Although many health care professionals use the term "drug screen" when they order a urine test for a panel of drugs of abuse including marijuana, the term "screening" applies to the evaluation of large populations regardless of clinical status, while the term "testing" refers to the evaluation of a single individual on the basis of clinical information or suspicion.

Although there are some preliminary studies and anecdotal reports which state that urine screening for marijuana and other drugs as a component of a comprehensive prevention program done in a non-punitive manner with attention to confidentiality does result in a decrease in marijuana use by adolescents, much more research is needed before any final judgments can be made. One of the problems with the available studies is that they include all students in a given grade or school, without regard to their marijuana or other drug use history, and compare them to themselves in a later year after screening was instituted or to students in another school. These studies do not differentiate the possible impact of such screening programs on the prevention of marijuana use in that population which has never or rarely used versus that population of adolescents who are already recurrent or frequent users. Thus, it remains to be shown, but would be of considerable importance, whether urine screening is an effective prevention component in either or both groups.

Treatment and Management

The management of an adolescent using marijuana will depend on many factors, all of which have goals of abstinence and completion of the developmental trajectory leading to a rewarding, fulfilling, and productive adult life. Because repeated marijuana use not only results in physiological and behavioral consequences but also interferes with the developmental process of adolescence, the management should include not only the individual but also the family, the school, peers, and the community [12]. Both the American Academy of Pediatrics and the American Society of Addiction Medicine have published a treatment recommendation protocol referred to as the "adolescent crosswalk" in which treatment recommendations are based on several factors at the time of assessment and diagnosis [20,21]. The factors center on the impact of the adolescent's use on his/her daily function [10,17,20,21]. It may take the form of office counseling and abstinence contracts with random urine testing to ensure compliance with the contract or may require a more intense and structured program of outpatient or even inpatient care followed by progressive reintroduction into family, school, and peer and community life. This is often a long term process which can severely stress financial, insurance, and emotional resources of the families.

Summary

Marijuana is a crude plant with over 400 chemical components. It is not an innocuous drug. The seriousness of the behavioral, emotional, and physiologic consequences is sufficient for all health care professionals, family members, school personnel, politicians, and others to recommend strongly against any use of marijuana by young people. These recommendations should be based on the known impact of marijuana use on the brain, including memory, learning, judgment, and possible psychiatric disease, as well as on the lung, the immune system, the endocrine and hormonal systems, trauma associated with acute intoxication, teratogenic potential, interference with motivation and the developmental processes of adolescence, and the known consequences of long-term use.

A discussion of marijuana and other drug use, including family use and attitudes, should be part of the routine periodic assessment of all preteens and adolescents. This assessment may be facilitated by the use of brief office screening tools such as the CRAFFT. Awareness of the adolescent's marijuana use as having broader family implications is essential.

The use of the laboratory and specifically urine testing should be guided by the principle that it is an adjunct to the evaluation and management of an individual who may be using marijuana and/or other drugs. It should be used with a knowledge of its benefits and limitations and, in general, with attention to confidentiality and patient consent. The role of urine screening for marijuana and other drugs as a part of a comprehensive substance abuse prevention program awaits further studies before wide implementation can be recommended. A key factor may be the impact on prevention in the non -using or rarely-using adolescents as compared to the recurrent and frequent users.

Referral and treatment should be directed to both the adolescent and the family. The level of care should be determined by the impact of the adolescent's use on him/herself and their family.

References

1. **Johnston LD, O'Malley PM, Bachman JG, and Schulenberg JE** (2006). Monitoring the Future: National Survey Results on Adolescent Drug Use: Overview of key findings, 2005, and tables from 1975-2005. (NIH Publication No. [Yet to be assigned].) Bethesda MD: National Institute on Drug Abuse. [online]. Available: www.monitoringthefuture.org; accessed 01/29/06

2. **American Academy of Pediatrics, Committee on Substance Abuse**. Marijuana: a continuing concern for pediatricians. Pediatrics. 1999; 104: 982-985. Available: www.aap.org

3. **American Academy of Pediatrics, Kulig JW and Committee on Substance Abuse.** Tobacco, Alcohol, and Other drugs: Role of the Pediatrician in Prevention, Identification, and Management of Substance Abuse. Pediatrics. 2005; 115: 816-821. Available: www.aap.org

4. **Shukla P,** Marijuana use in children and adolescents. UpToDate® [on-line by subscription]. Available: www.uptodate.com; accessed 01/29/06

5. **Weaver M,** Marijuana use in adults. UpToDate® [on-line by subscription]. Available: www.uptodate.com; accessed 01/29/06

6. **Hawkins JD,** Risk and Protective Factors and their Implications for Preventive Interventions for the Health Care Professional. In: Schydlower M, ed. Substance Abuse: A Guide for Health Professionals. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2002: pgs 1-19

7. **Comerci G,** The Role of the Primary Care Physician. In: Schydlower M, ed. Substance Abuse: A Guide for Health Professionals. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2002: pgs 21-41

8. **Anglin TM,** Evaluation by Interview and Questionnaire. In: Schydlower M, ed. Substance Abuse: A Guide for Health Professionals. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2002: pgs 43-103

9. **Rosenfeld W and Wingert WE,** Scientific Issues in Drug Testing and Use of the Laboratory. In: Schydlower M, ed. Substance Abuse: A Guide for Health Professionals. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2002: pgs 105-121

10. **Fuller PG,** The Role of the Primary Care Physician in the Referral Process. In: Schydlower M, ed. Substance Abuse: A Guide for Health Professionals. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2002: pgs 123-141

11. **Brown RT,** Risk Factors for Substance abuse in Adolescents. In: Rogers PD and Heyman RB, eds. Addiction Medicine: Adolescent Substance Abuse. Pediatric Clinics of North America. April 2002. vol. 49: pgs 247-255

12. **Kodjo CM and Klein JD,** Prevention and Risk of Adolescent Substance abuse: The Role of Adolescents, Families and Communities. In: Rogers PD and Heyman RB, eds. Addiction Medicine: Adolescent Substance Abuse. Pediatric Clinics of North America. April 2002. vol. 49: pgs 257-268

13. **Dias P,** Adolescent Substance Abuse: Assessment in the Office. In: Rogers PD and Heyman RB, eds. Addiction Medicine: Adolescent Substance Abuse. Pediatric Clinics of North America. April 2002. vol.49: pgs 269-300

14. **Weddle M and Kokotailo P,** Adolescent Substance Abuse: Confidentiality and Consent. In: Rogers PD and Heyman RB, eds. Addiction Medicine: Adolescent Substance Abuse. Pediatric Clinics of North America. April 2002. vol.49: pgs 301 -315

15. **Casavant M,** Urine Drug Screening in Adolescents. In: Rogers PD and Heyman RB, eds. Addiction Medicine: Adolescent Substance Abuse. Pediatric Clinics of North America. April 2002. vol.49: pgs 317-327

16. **Levy S, Vaughan BL, and Knight JR,** Office-Based Intervention for Adolescent Substance Abuse. In: Rogers PD and Heyman RB, eds. Addiction Medicine: Adolescent Substance Abuse. Pediatric Clinics of North America. April 2002. vol.49: pgs 329-343

17. **Jaffe SL,** Treatment and Relapse Prevention for Adolescent Substance Abuse. In: Rogers PD and Heyman RB, eds. Addiction Medicine: Adolescent Substance Abuse. Pediatric Clinics of North America. April 2002. vol. 49: pgs 345-352

18. **Gruber AJ and Pope Jr. HG,** Marijuana Use Among Adolescents. In RogersPD and Heyman RB, eds. Addiction Medicine: Adolescent Substance Abuse. Pediatric Clinics of North America. April 2002. vol.49: pgs 389-413

19. **Knight JR, Sherritt L, Shrier LA, Harris SK, and Chang G,** Validity of the CRAFFT substance abuse screening test among adolescent clinic patients. Archives of Pediatrics and Adolescent Medicine. 2002. vol.156: pgs 607-614

20. **Graham AW and Schlutz TK, eds.** Adolescent Criteria: Crosswalk of Levels 0.5 through IV. Principles of Addiction Medicine, 2nd ed. American Society of Addiction Medicine. 1998. pg 1298

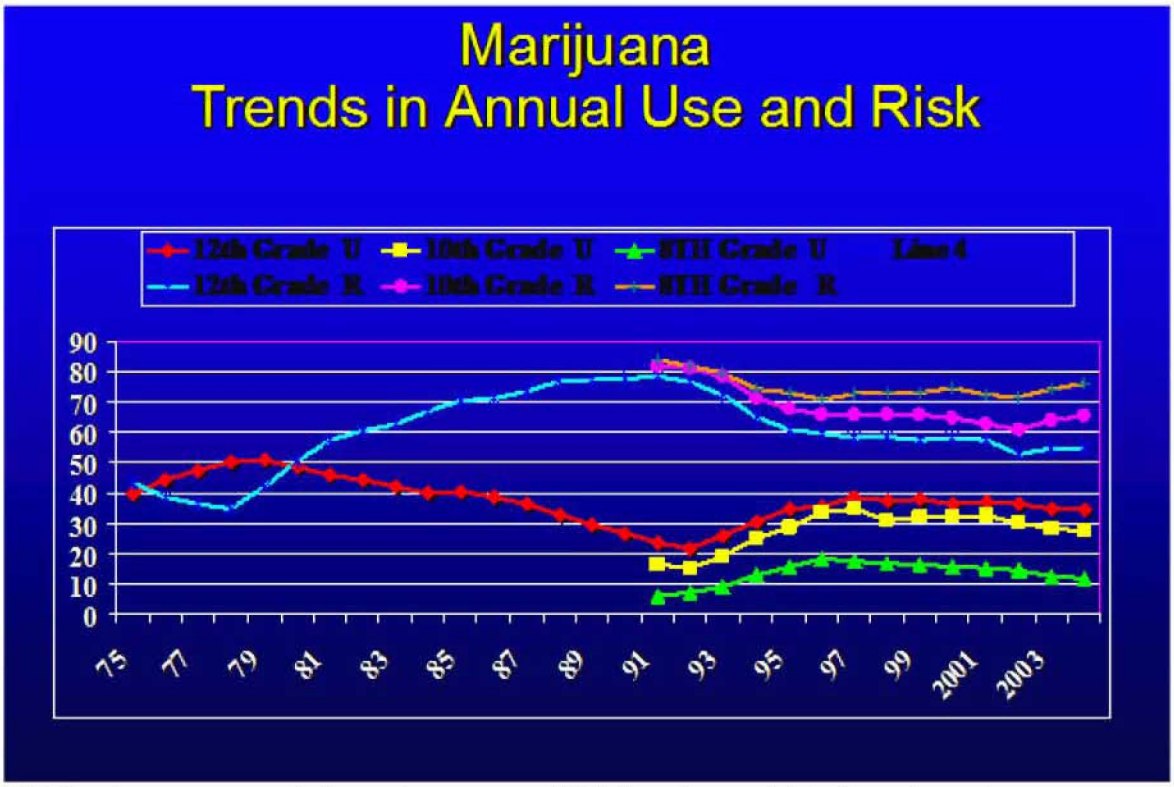
21. **American Academy of Pediatrics,** Committee on Substance Abuse. Indications for Management and Referral of Patients Involved in Substance abuse. Pediatrics. vol. 106: pgs 143-148. Available: www.aap.org

22. **American Academy of Pediatrics,** Committee on Substance Abuse. Legalization of Marijuana: Potential Impact on Youth. Pediatrics. vol. 113: pgs1825-1826. Available: www.aap.org

23. **Coupey, SM**, Specific Drugs. In: Schydlower M, ed. Substance Abuse: A Guide for Health Professionals. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2002: pgs 199-207

Appendix

Figure 1. Marijuana Trends in Annual Use and Risk [1]



USE: % using once or more in the past year **RISK: % saying great risk of harm in regular use**

TABLE 1. CRAFFT: Questions to Identify Adolescents With Substance Abuse Problems [19]

C	Have you ever ridden in a *c*ar driven by someone (including yourself) who was "high" or had been using alcohol or drugs?
R	Do you ever use alcohol or drugs to *r*elax, feel better about yourself, or fit in?
A	Do you ever use alcohol or drugs while you are by yourself, or *a*lone?
F	Do you ever *f*orget things you did while using alcohol or drugs?
F	Do your family or *f*riends ever tell you that you should cut down on your drinking or drug use?
T	Have you ever gotten into *t*rouble while you were using alcohol or drugs?

Two or more "yes" answers suggest that the adolescent may have a serious problem with substance abuse, and additional assessment is warranted.