A Pharmacy and Therapeutics Perspective on Medical Marijuana Use in the Canadian Health Care System

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ABSTRACT

In 2001, the Ontario Hospital Association invited hospitals to discuss whether individual facilities should allow the use of medical marijuana. This communication prompted the Pharmacy and Therapeutics Committee of Sunnybrook and Women's College Health Sciences Centre to discuss the issue at its monthly meeting in November 2001. The Committee outlined some of the uncertainties of marijuana use in the medical setting (e.g., efficacy, safety, distribution, quality, and legal status). Various associations of health care professionals have issued regulations and recommendations to their members and guidance regarding incorporation of these recommendations in the hospital setting. The Pharmacy and Therapeutics Committee at Sunnybrook and Women's College Health Sciences Centre decided not to allow the use of medical marijuana at its facility. The group recognized that marijuana use is a complex issue that continues to be debated at both national and international levels. The publication of original data and possible changes in guidelines and legislation may challenge the decisions rendered by hospitals in Ontario and the rest of Canada.

Key words: medical marijuana, policy, hospitals, health care professionals

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RÉSUMÉ

En 2001, l'Ontario Hospital Association a invité les hôpitaux à débattre l'utilisation de la marijuana à des fins médicales dans les établissements de santé. Cette communication a amené le Comité de pharmacologie et de thérapeutique du Sunnybrook and Women's College Health Sciences Centre à discuter de cette question à sa réunion mensuelle en novembre 2001. Le Comité a émis des réserves quant au bien-fondé de l'utilisation de la marijuana dans le milieu des soins de santé (p. ex., aux plans de l'efficacité, de l'innocuité, de la distribution, de la qualité et des aspects légaux). Diverses associations de professionnels de la santé ont émis des normes et des recommandations à l'intention de leurs membres, ainsi que des lignes directrices sur l'application de ces recommandations dans les hôpitaux. Le Comité de pharmacologie et de thérapeutique du Sunnybrook and Women's College Health Sciences Centre a décidé de ne pas permettre l'utilisation intra-muros de la marijuana à des fins médicales. Le Comité a reconnu que l'utilisation de la marijuana est un sujet complexe qui fait toujours l'objet de débats au niveau national et international. La publication de nouvelles données et les modifications possibles aux lignes directrices et aux lois pourraient remettre en question les décisions qu'ont prises les hôpitaux en Ontario et dans le reste du Canada.

Mots clés : marijuana à des fins médicales, politiques, hôpitaux, professionnels de la santé

INTRODUCTION

Canada was the first country to regulate and allow marijuana use for medical purposes, through Health Canada's Office of Cannabis Medical Access (OCMA). The newly established Marihuana Medical Access Regulations (MMAR) provide a compassionate framework whereby people with terminal illnesses or serious symptoms associated with specific medical conditions are allowed to use marijuana. The OCMA has specified that people who fall into 1 of 3 categories may apply for authorization to possess a supply of marijuana for medical use (Table 1).[1] A medical practitioner must authorize and provide a medical history for each application. Patients who are granted permission to use marijuana for medical purposes are given an identification card (with a photograph) and are allowed to possess a 30-day supply of the substance. According to Health Canada, as of Feburary 2004, 717 people had been "allowed to possess marihuana for medical purposes".[2] MMAR authorizations have been issued in every province and are roughly equal, on a per capita basis, in each province, with the exceptions of Quebec (authorizations less than the average per population), Nova Scotia (authorizations greater than the average per population), and the combined group of Yukon, Prince Edward Island, Nunavut, and the Northwest Territories (authorizations greater than the average per population). The OCMA also grants cultivation and production licences for growing marijuana for medical purposes; 537 such licences had been granted as of February 2004.[2]

The Pharmacy and Therapeutics Committee at the authors' institution discussed the use of medical marijuana in November 2001, after the MMAR came into force on July 30, 2001.[3] Then, in October 2002, the Ontario Hospital Association Professional Advisory Committee released a report to assist hospitals in gaining a better understanding of the implications of medical marijuana use. The following are highlights of their advice on key issues:[4]

- It is recommended that hospitals seek legal advice from their own legal counsel.
- It is acceptable that an institution may prohibit a patient from possessing marijuana within a hospital environment according to the Regulatory Impact Analysis Statement which was published with Marihuana Medical Access Regulations, and the hospital does not breach the standards of hospital care if it treats patients with diseases who are eligible for medical use of marijuana.

Table 1. Categories of Authorization for Medical Marijuana[1]

Category	Description
1	Applicants who have a terminal illness with a projected lifespan of less than 12 months
2	Applicants who suffer from specific symptoms associated with certain serious medical conditions
	Multiple sclerosis: severe pain and/or persistent muscle spasms
	Spinal cord injury: severe pain and/or persistent muscle spasms
	Spinal cord disease: severe pain and/or persistent muscle spasms
	Cancer: severe pain, cachexia, anorexia, weight loss, and/or severe nausea
	AIDS/HIV infection: severe pain, cachexia, anorexia, weight loss, and/or severe nausea
	Severe forms of arthritis: severe pain
	Epilepsy: seizures
3	Applicants who have symptoms associated with a serious medical condition, other than those described in categories 1 and 2, for which conventional treatments have failed to relieve symptoms

AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus.

- Hospitals and health care professionals should consider obtaining a specific waiver or release from liability from each patient who uses medicinal marijuana, to document that informed consent discussions have occurred.
- Hospitals and health care professionals are responsible for taking reasonable steps to evaluate the safety of other patients, including the risks associated with smoke exposure and the possibility of fire when a patient is using marijuana.
- If a patient is permitted to use marijuana for medical purposes, the hospital should request that the patient keep only a limited quantity on hand and ensure that the patient's room, locker, or bedside table has an effective lock.
- It is recommended that health care professionals not become involved in the administration of marijuana and that the patient should self-administer.

After lengthy discussion, the Pharmacy and Therapeutics Committee at the authors' institution did not approve the use of marijuana at its facility. This decision had less to do with the availability of clinical evidence than with the medical, legal, and logistic issues related to administration and distribution of marijuana. The majority of comments within the Committee were related to the uncertainties associated with the use of marijuana in the medical environment. This paper

discusses issues related to the quality, distribution, clinical efficacy, and adverse effects of medical marijuana; its impact on health care professionals and health care facilities; and its economic implications.

QUALITY

The quality or grade of marijuana being used by patients is unknown if they have grown it themselves, have had a designated person grow it, or have purchased it illegally. Marijuana, a mixture of flowering tops and leaves from the plant *Cannabis sativa*, consists of many active compounds, which vary in proportion from one plant to another.[5-8] This variability may lead to differences in dosing, quantity, and quality.[6,9]

Delta-9-tetrahydrocannabinol (THC) is the main psychoactive cannabinoid in marijuana. The concentration of THC in marijuana varies greatly depending on growing conditions, plant genetics, and methods of processing after harvest.[5,6,8,10] Concentrations of THC in marijuana typically range from 0.3% to 4% by weight. Specially grown and selected marijuana may contain more than 15% THC. Therefore, a marijuana cigarette weighing 1 g might contain as little as 3 mg of THC or as much as 150 mg or more.

To address the issue of quality control, Health Canada awarded a $5.7 million contract to Prairie Plant Systems (PPS) for the production and harvest of a reliable source of high-quality, standardized, research-grade marijuana to meet the Health Canada recommendation of 5% THC content.[11] Recent reports have suggested that the quality of the marijuana from PPS is suboptimal.[12] Laboratory tests conducted by a patients' rights organization, Canadians for Safe Access, showed that the Health Canada marijuana contained only 3% THC whereas its comparator, marijuana grown by the Vancouver Island Compassion Club Society (VICCS), contained over 12% THC. Additional testing revealed that the arsenic and lead contents in the government sample were much higher than in the sample from the VICCS. Numerous reports regarding "sticks and stems" and a dry, powdery substance were communicated to Health Canada by patients. The consequences of poor quality may increase the amount of inhaled marijuana required to achieve an appropriate medical effect. Currently, 121 medical users in Canada are permitted to buy Health Canada marijuana (dried and seeds).[2]

DISTRIBUTION

At present, the options for acquiring marijuana for medical use include obtaining a licence to grow the plants, designating another individual or company to grow the plants, or purchasing from illicit sources. In the Netherlands, the Government Bureau for Medicinal Cannabis has allowed pharmacies to dispense and sell medical marijuana to patients with prescriptions; however, Canadian pharmacies cannot dispense medical marijuana.[13] It has been proposed that physicians should dispense mature marijuana or marijuana seeds to authorized individuals.[14]

It is unclear who will be responsible for the packaging, shipping, and delivery of marijuana seeds and mature cannabis from authorized government growers across the country. It is questionable whether Canada Post or courier companies will be eager to distribute marijuana to patients with a potential threat of prosecution for shipping illegal substances or without added insurance for protection from loss and theft. Health Canada marijuana is distributed by courier in 30-g bags at a cost of $150.[15]

CLINICAL EFFICACY

Much of the clinical evidence for the efficacy of inhalational medical marijuana is derived from anecdotal accounts (patient self-reports or physician case reports).[16] Health Canada has not approved marijuana as a therapeutic product, but 2 synthetic THC preparations are available for oral administration in Canada: dronabinol (indicated for the treatment of chemotherapy-induced emesis and for appetite stimulation in AIDS-related anorexia associated with weight loss) and nabilone (indicated for the treatment of nausea and vomiting caused by cancer chemotherapy). A case could be made that people who smoke marijuana could use these oral medications instead.

The optimal doses and routes of marijuana administration have not been established. Health Canada has suggested a maximum daily dose of 5 g of dried marijuana in the application form,[1] although optimal dosing will be variable across the population of patients with approval for marijuana use, in consideration of naïve versus experienced users and quality and quantity of marijuana used. Dronabinol has extensive first-pass metabolism, with only 10% to 20% systemic availability of THC,[17] whereas absorption of the THC in marijuana cigarettes can vary widely and therefore peak plasma THC concentrations vary widely among individuals.[18] Smoking marijuana provides faster onset of psychoactive effects (the "high") than oral ingestion, which indicates why smoking is the preferred route for many people.[19] THC has also been administered as a suppository,

which resulted in higher plasma THC concentrations (almost twice the bioavailability) than from oral administration in a pilot study.[20] Other routes of administration under investigation include sublingual sprays or tablets, nebulization, and aerosols.[21] Although randomized controlled trials of marijuana have been conducted for various clinical diagnoses, a comprehensive review for the UK Department of Health found that only 4 trials involved patients who ingested THC by smoking marijuana rather than an oral form of THC.[21]

ADVERSE EVENTS

All health care professionals approving and distributing marijuana for medical purposes should monitor drug interactions, adverse drug reactions, and long-term effects associated with medical marijuana (summarized in Table 2).[22-37] The absorption or metabolism of concomitant drugs may be affected by the administration of marijuana. For example, THC may delay gastric emptying[22] or it may compete for protein-binding sites of other highly bound drugs,[23] thus affecting absorption of other drugs. THC is metabolized hepatically by the cytochrome P450 (CYP) system and has been shown to induce the CYP isozymes CYP1A1 and CYP1A2[24,25] and to inhibit the CYP isozymes CYP3A4 and CYP3A11,[26,27] which may alter the metabolism of agents that are substrates for these pathways.

Since July 2003, health care professionals have been able to access Health Canada's comprehensive on-line summary of peer-reviewed literature and international reviews concerning medical marijuana, including potential harmful effects.[23] This document is comparable to the 1999 US Institute of Medicine's report,[38] which also evaluated the scientific evidence for benefits and risks of using marijuana as a medical product.

Five general safety precautions can be found in Table 2.[23] Major concerns about adverse effects of marijuana and THC relate to long-term use[28,29] and cognition,[39-42] as well as prenatal exposure and possible teratogenicity for women of child-bearing age.[33-37,43] The adverse effects on other health conditions — respiratory,[28-32,44] cardiovascular,[26,45-48] and the immune system[49-51] — must also be monitored, especially in special populations such as elderly people, children, and pregnant women.

Table 2. Potential Drug Interactions and Adverse Events Associated with Use of Medical Marijuana

Type of Problem	Description of Problem
Drug interactions	THC slows gastric emptying time[22] and can slow absorption of ethanol, antidepressants, barbiturates, and opiates THC is highly bound to plasma proteins and may compete for binding sites of other highly bound drugs, altering pharmacokinetics of therapeutic agents[23]
Metabolism	THC can induce CYP1A1 and CYP1A2[24,25] THC can inhibit CYP3A4 and CYP3A11[26,27]
Safety	Smoking marijuana is not recommended for people with respiratory insufficiencies such as asthma or COPD[23] Marijuana use in general is not recommended for people with a history of substance abuse, because marijuana is itself an abused substance[23] Marijuana use should be monitored in patients with psychiatric disorders (e.g., schizophrenia, depression, mania) because of the possibility of exacerbation of symptoms[23] Marijuana should be used with caution in patients with cardiac disorders, because of its occasional effects on the cardiovascular system (e.g., hypotension, tachycardia)[23] Marijuana impairs cognition involving short-term memory, attention, and concentration (e.g., impaired driving)[23]
Long-term effects	Heavy, long-term marijuana smokers may experience bronchitis, wheezing, phlegm production, and chronic cough, as well as increased risk of COPD[23,28-30] Histopathology results show hyperplasia and inflammation of airway cells[31,32] Prolonged and repetitive use of marijuana may lead to tolerance and to psychological and physical dependence (chronic users may suffer various degrees of cognitive impairment that may be permanent)[23] Marijuana and its metabolites have a long half-life and therefore elimination from the body is slow[23]
Teratogenicity	The results of human epidemiological studies are conflicting, with some reporting reduced birth weight[33] and others reporting no effect on birth weight[34] among women who smoked marijuana during pregnancy Longitudinal investigations suggest that in utero exposure has a negative impact on attention behaviour and visual analysis or hypothesis testing but not on standardized derived IQ[35,36] Exposure to marijuana through the mother's milk in the first month after birth was associated with a decrease in infant motor development at 1 year of age[37]

THC = Δ-9-tetrahydrocannabinol, COPD = chronic obstructive pulmonary disease, IQ = intelligence quotient.

IMPACT ON HOSPITAL FACILITIES

One major challenge in allowing use of medical marijuana in the hospital setting is determining how such use can be incorporated into patient care. For example, can marijuana be treated in the same way as other medications that a patient might use during the hospital stay? In some institutions, patients receive only medications that have been prescribed during the hospital stay, whereas in others, patients are allowed to bring medications from home. In the latter situation, patients could bring marijuana from their home supply. Consequently, hospitals must have systems for storing, distributing, and clinically evaluating the marijuana. Moreover, marijuana prescriptions should clearly indicate the dose, dosing interval, and route of administration, as is done for other all other medications. Administration, storage, and the effects of second-hand marijuana smoke are complex issues that have not been addressed by the OCMA but that must be dealt with by hospitals where marijuana might be used by patients.

Each hospital site will probably seek legal counsel regarding use of medical marijuana, for the protection of staff and patients. Questions to be answered include the following: If a hospital allows marijuana use on its grounds, who among the hospital employees would be responsible for verifying that the marijuana users had the appropriate authorization? Would the police department target the hospital or arrest hospital employees and patients for possession exceeding legal amounts of marijuana for personal or medical use and possible illegal distribution? Who would be liable if a patient's marijuana was stolen? The small number of legal rulings by federal and provincial courts to date regarding the liability aspects of marijuana utilization remain unclear.

IMPACT ON HEALTH CARE PROFESSIONALS

Because of a lack of consensus in the peer-reviewed literature, health care professionals will have difficulty in determining recommended doses, duration of therapy, dosage forms, and routes of administration for medical marijuana and will also have problems in monitoring adverse events.

The Ontario College of Pharmacists has stated that hospital and community pharmacists will not be directly affected by the regulations for personal possession or production, but the College has advised pharmacists to be aware of drug interactions or adverse drug reactions related to marijuana use for approved medical conditions.[52] However, when patients seek advice regarding medical marijuana from pharmacists while in hospital or visiting a pharmacy, pharmacists are put in the difficult position of not knowing what the patient has been told by other health care professionals; furthermore, it is unclear how drug interactions or adverse reactions should be reported, given that marijuana is not approved by Health Canada.

A physician must approve any application to the OCMA for use of medical marijuana. In doing so, the physician is indicating that the benefits of the marijuana outweigh its risks (such as the harms associated with smoking in general and the adverse events of marijuana). Both the College of Physicians and Surgeons of Ontario[53] and the Ontario Medical Association[54] oppose the new regulations because of the lack of scientific evidence available to guide physicians in appropriate prescribing of marijuana.

Neither the Canadian Nurses Association nor the Canadian Association of Nurses in Oncology has taken a position on the medical use of marijuana. Given that nursing practice involves a variety of roles, including provision of direct care and patient education, the lack of specific positions by these organizations puts nurses in the difficult position of not being able to give patients even basic information about medical marijuana. The College of Nurses of Ontario (CNO) has addressed the issue of medical marijuana in its newsletter, stating that nurses "participating in the administration of medical marijuana are not in violation of any of CNO's standards" and "that the decision to allow a client to possess and/or grow marijuana within an institution remains the decision of that facility".[55]

ECONOMIC IMPLICATIONS

From a hospital perspective, there could be considerable expense associated with the adoption of a marijuana utilization policy. The costs associated with construction, insurance, supervision, and cleaning of designated smoking areas would be significant. The costs of providing locked storage facilities for patients and occupational hazard training for hospital personnel must also be considered. From the perspective of a health system payer, additional costs may be incurred if pharmacists charge a dispensing fee (in the event that marijuana is eventually distributed by community pharmacies) or if physicians receive reimbursement for their authorization and dispensing of medical marijuana. Appropriate coding and organizational infrastructure for these reimbursement mechanisms need to be put into place.

EVALUATION OF MARIJUANA UTILIZATION

Currently, there is no method to determine the clinical or medical "value" of this new legislation. Once a person has received approval to use medical marijuana, there is no follow-up on patient outcomes. A formal, prospective system of collecting data from all MMAR-approved patients is needed to determine whether the program improves patient symptoms (e.g., decreases pain), outcomes, and quality of life. Monitoring marijuana use will provide evidence on quantity, sources, and frequency of use. These data should be collected routinely as part of a "post-policy surveillance" program and should be used to update and evaluate the merits and challenges of medical marijuana programs like the OCMA.

RECENT UPDATES

Canada may become the second country in the world to distribute marijuana through pharmacies. In March 2004, Health Canada announced that it was organizing a pilot project in British Columbia to allow medical users to purchase marijuana in specified community pharmacies. This distribution system was adapted from a similar program model in the Netherlands. The College of Pharmacists of British Columbia released a statement indicating that it supports patient access to standardized medical marijuana through pharmacies, preferably at the same level of control as synthetic cannabinoids.[56]

CONCLUSIONS

The use of marijuana for terminal illnesses and symptom relief presents complex problems. Medical and legal issues regarding marijuana use continue to be debated at the national and international levels. There is a need for more guidelines on the use of marijuana in the medical arena. Other countries will be watching Canada to determine the merits and challenges of this country's new legislation.

While decision makers have been focusing on the distribution of medical marijuana, the broader implications for health care professionals and the health care system at large have not been discussed in great detail and essentially remain unresolved. Health professional regulatory agencies have expressed concerns regarding decisions about marijuana use, noting that there remains a paucity of scientific evidence about the efficacy and safety of inhaled cannabinoids.

There is a need for efficacy and safety information on inhaled or smoked marijuana. As mentioned previously, Health Canada has published a report outlining the information on dosing, administration, efficacy, and safety available for marijuana.[23] In July 2001, a peer-reviewed clinical trial examining the effects of smoked cannabis for chronic neuropathic pain in a non-HIV or multiple sclerosis population received funding from Health Canada in partnership with the Canadian Institutes of Health Research (CIHR).[57] The quality and intensity of pain will be assessed, and the results from this study may provide support for other investigators to design larger and more conclusive studies in the future. In the United States, the Center for Medicinal Cannabis Research has initiated 5 clinical trials, including a safety trial of smoked marijuana.[58]

References

1. Application for authorization to possess dried marihuana. Ottawa (ON): Health Canada; [date unknown]. Available at: http://www.hc-sc.gc.ca/hecs-sesc/ocma/pdf/completesection.pdf. Accessed 2004 May 3. 25 p.
2. Office of Cannabis Medical Access. Marihuana for medical purposes — statistics (February 6, 2004). Ottawa (ON): Health Canada; modified 2004 Feb 23. Available at: http://www.hc-sc.gc.ca/hecs-sesc/ocma/stats/2004/feb/stats_feb-04.htm. Accessed 2004 May 3.
3. Notification of passage of regulations: Controlled Drugs and Substances Act — Marihuana Medical Access Regulations. Regulations amending the Narcotic Control Regulations. Ottawa: Health Canada; 2001 Jun 15. Available at: http://www.hc-sc.gc.ca/hecs-sesc/controlled_substances/pdf/regulations/marihuana_06-13-01.pdf. Accessed 2004 May 3. 67 p.
4. A report on the Marihuana Medical Access Regulations. Toronto (ON): Ontario Hospital Association; 2002 Oct 16. Available at: http://www.oha.com/oha/capi.nsf/f2686cfb08acbc4885256c980064f442/39e2c43fd10aed9785256ca70074e6d9/$FILE/Medica%20Marijuana%20-%20Final%20Oct%2018.pdf. Accessed 2004 May 3. 7 p.
5. Agurell S, Dewey WL, Willett RE, editors. *The cannabinoids: chemical, pharmacologic, and therapeutic aspects*. New York: Academic Press; 1984.
6. Graham JDP, editor. *Cannabis and health*. New York: Academic Press; 1976.
7. Jones RT. Drug of abuse profile: cannabis. *Clin Chem* 1987; 33(11 Suppl):72B-81B.
8. Mechoulam R, editor. *Marijuana: chemistry, pharmacology, metabolism and clinical effects*. New York: Academic Press; 1973.
9. Agurell S, Halldin M, Lindgren JE, Ohlsson A, Widman M, Gillespie H, et al. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev* 1986;38(1):21-43.
10. Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 1996;91:1585-614.
11. Prairie Plant Systems Inc. Ottawa (ON): Health Canada; modified 2003 Jun 16. Available at: http://www.hc-sc.gc.ca/hecs-sesc/ocma/information3.htm. Accessed 2004 May 3.

12. MedicalMarihuana.ca staff. Lab tests reveal Health Canada government weed weak. Duncan (BC): BCC Communications Inc.; 2003 Sep 15. Available at: http://www.medicalmarihuana.ca/govtpot.html. Accessed 2004 Apr 30.
13. Paul Gallagher. Dutch make pot a prescription drug. [place unknown]: Reuters News Agency; 2003 Sep 1. Available at: http://www.medicalmarihuana.ca/nlpharmacy.html. Accessed 2004 Apr 30.
14. Spurgeon D. Canadian doctors question marijuana for medicinal use. *BMJ* 2003;327:122.
15. CBC News Online staff. Medical marijuana headed for pharmacies. Toronto (ON): CBC; updated 2004 Mar 22. Available at: http://www.cbc.ca/stories/2004/03/21/canada/marijuana_040321. Accessed 2004 May 3.
16. Martin BR, Lichtman AH. Cannabinoid transmission and pain perception. *Neurobiol Dis* 1998;5(6 Pt B):447-61.
17. C*ompendium of pharmaceuticals and specialties*. Ottawa (ON): Canadian Pharmacists Association; 2003. p. 949.
18. Perez-Reyes M. Marijuana smoking: factors that influence the bioavailability of tetrahydrocannabinol. *Natl Inst Drug Abuse Res Monogr* 1990;99:42-62.
19. Iversen LL. *The science of marijuana*. Oxford: Oxford University Press; 2000. p. 46-7.
20. Brenneisen R, Egli A, Elsohly MA, Henn V, Spiess Y. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. *Int J Clin Pharmacol Ther* 1996;34:446-52.
21. Robson P. Therapeutic aspects of cannabis and cannabinoids. *Br J Psychiatry* 2001;178:107-15.
22. McCallum RW, Soykan I, Sridhar KR, Ricci DA, Lange RC, Plankey MW. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind, randomized study. *Aliment Pharmacol Ther* 1999;13:77-80.
23. Information for health care professionals: marihuana (marijuana, cannabis). Ottawa: Health Canada; 2003. Available: http://www.hc-sc.gc.ca/hecs-sesc/ocma/pdf/marihuana.pdf. Accessed 2004 May 3. 54 p.
24. Zullino D, Delessert D, Eap C, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine and olanzapine [abstract]. *Int Clin Psychopharmacol* 2002;17:141-3.
25. Roth M, Marques-Margallanes J, Yuan M, Sun W, Tashkin D, Hankinson O. Induction and regulation of the carcinogen-metabolizing enzyme CYP1A1 by marijuana smoke and delta(9)-tetrahydrocannabinol [abstract]. *Am J Respir Cell Mol Biol* 2001;24:339-44.
26. McLeod A, McKenna C, Northbridge D. Myocardial infarction following the combined recreational use of Viagra and cannabis. *Clin Cardiol* 2002;25(3):133-4.
27. Bornheim L, Grillo M. Characterization of cytochrome P450 3A inactivation by cannabidiol: possible involvement of cannabidiol-hydroxyquinone as a P450 inactivator [abstract]. *Chem Res Toxicol* 1998;11:1209-16.
28. Hubbard JR, Franco SE, Onaivi ES. Marijuana: medical implications. *Am Fam Physician* 1999;60:2583-8,2593.
29. Hall W, Solowij N. Adverse effects of cannabis. *Lancet* 1998;352:1611-6.
30. Taylor DR, Fergusson DM, Milne BJ, Horwood LJ, Moffitt TE, Sears MR, et al. A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction* 2002;97:1055-61.
31. Fligiel SE, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest* 1997;112:319-26.
32. 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;157:928-37.
33. Zuckerman B, Frank DA, Hingson R, Amaro H, Levenson SM, Kayne H, et al. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989;320:762-8.
34. Shiono PH, Klebanoff MA, Nugent RP, Cotch MF, Wilkins DG, Rollins DE, et al. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. *Am J Obstet Gynecol* 1995;172:19-27.
35. Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol* 1999;21:513-25.
36. Richardson GA, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. *Neurotoxicol Teratol* 2002;24:309-20.
37. Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. *Neurotoxicol Teratol* 1990;12:161-8.
38. First, do no harm: consequences of marijuana use and abuse. In: Joy JE, Watson SJ, Benson JA Jr, editors. *Marijuana and medicine: assessing the science base*. Washington (DC): National Academies Press; 1999. p. 83-136.
39. Rogers RD, Robbins TW. Investigating the neurocognitive deficits associated with chronic drug misuse. *Curr Opin Neurobiol* 2001;11:250-7.
40. Fletcher JM, Page JB, Francis DJ, Copeland K, Naus MJ, Davis CM, et al. Cognitive correlates of long-term cannabis use in Costa Rican men. *Arch Gen Psychiatry* 1996;53:1051-7.
41. Block RI, Ghoneim MM. Effects of chronic marijuana use on human cognition. *Psychopharmacology* 1993;110:219-28.
42. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA* 1996;275:521-7.
43. Stern L. In vivo assessment of the teratogenic potential of drugs in humans. *Obstet Gynecol* 1981;58(5 Suppl):3S-8S.
44. Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, et al. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marihuana and tobacco, smokers of tobacco alone, and nonsmokers. *Am Rev Respir Dis* 1987;135:209-16.
45. Benowitz NL, Jones RT. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *J Clin Pharmacol* 1981;21(8-9 Suppl):214S-223S.
46. Benowitz NL, Jones RT. Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clin Pharmacol Ther* 1975;18:287-97.
47. Graham JDP. The cardiovascular action of cannabinoids. In: Mechoulam R, editor. *Cannabinoids as therapeutic agents*. Boca Raton (FL): CRC Press; 1986. p. 159-66.
48. Kelly TH, Foltin RW, Fischman MW. Effects of smoked marijuana on heart rate, drug ratings and task performance by humans. *Behav Pharmacol* 1993;4:167-78.
49. Cabral G. Marijuana and cannabinoids: effects on infections, immunity, and AIDS. *J Cannabis Ther* 2001;1:61-85.
50. Klein TW, Newton CA, Friedman H. Cannabinoids and the immune system. *Pain Res Manage* 2001;6(2):95-101.

51. Bredt BM, Higuera-Alhino D, Shade SB, Hebert SJ, McCune JM, Abrams DI. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *J Clin Pharmacol* 2002;42(11 Suppl):82S-89S.

52. Ujiye G. Marihuana Medical Access Regulations. Toronto (ON): Ontario College of Pharmacists; [date unknown]. Available at: http://www.ocpinfo.com/client/ocp/OCPHome.nsf/web/Marijuana+Medical+Access!OpenDocument. Accessed 2004 May 5.

53. Policy #3-02: Prescribing medical marijuana. Toronto (ON): College of Physicians and Surgeons of Ontario; 2002 Sep/Oct. Available at: http://www.cpso.on.ca/Policies/marijuana.htm. Accessed 2004 May 5.

54. Mendel J. OMA advances medical marijuana concerns to federal health minister. Toronto (ON): Ontario Medical Association; 2001 Dec. Available at: http://www.oma.org/pcomm/OMR/dec/01marijuana.htm. Accessed 2004 May 5.

55. Cyr M. Medical marihuana, confidentiality in occupational nursing, buying coffee for a client. *Coll Nurses Ont Commun* 2001;26(4):16.

56. PPP-51: Medical marijuana. In: Professional practice policies. Victoria (BC): College of Pharmacists of British Columbia; approved 2003 Sep 19. Available at: http://www.bcpharmacists.org/pdf/pgp4ppp.pdf. Accessed 2004 Apr 29.

57. Rock announces funding for first-ever marijuana clinical trial in Canada [press release]. Ottawa (ON): Canadian Institutes of Health Research; 2001 Jul 26. Available at: http://www.cihr-irsc.gc.ca/ e/news/7931.shtml. Accessed 2004 May 5.

58. Vastag B. Medical marijuana center opens doors. *JAMA* 2003;290:877-9.

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