IN THE HIGH COURT OF SOUTH AFRICA
GAUTENG DIVISION, PRETORIA

CASE NO: 58668/2011

In the matter between:

JULIAN CHRISTOPHER STOBBS	**FIRST PLAINTIFF**
KATHLEEN (MYRTLE) CLARKE	**SECOND PLAINTIFF**
CLIFFORD ALAN NEAL THORP	**THIRD PLAINTIFF**
and	
NATIONAL DIRECTOR OF PUBLIC PROSECUTIONS	**FIRST DEFENDANT**
MINISTER OF JUSTICE AND CONSTITUTIONAL DEVELOPMENT	**SECOND DEFENDANT**
MINISTER OF HEALTH	**THIRD DEFENDANT**
MINISTER OF SOCIAL DEVELOPMENT	**FOURTH DEFENDANT**
MINISTER OF INTERNATIONAL RELATIONS AND COOPERATION	**FIFTH DEFENDANT**
MINISTER OF TRADE AND INDUSTRY	**SIXTH DEFENDANT**
MINISTER OF POLICE	**SEVENTH DEFENDANT**
DOCTORS FOR LIFE INTERNATIONAL INCORPORATED	**EIGHTH DEFENDANT**

PLAINTIFFS' NOTICE IN TERMS OF RULE 36(9)(b)
in respect of Donald I. Abrams M.D.

TAKE NOTICE THAT, as indicated in their Notice in terms of Rule 36(9)(a) dated **2 December 2015**, the Plaintiffs intend to call **DONALD I. ABRAMS** (*"the expert"*) to give evidence as an expert in this matter.

TAKE FURTHER NOTICE that the Expert's *curriculum vitae* is annexed hereto and marked **"A"**. A summary of the expert's relevant qualifications is, *inter alia*, as follows: -

1. The expert is chief of the Haematology-Oncology Division at San Francisco General Hospital and a Professor of Clinical Medicine at the University of California San Francisco ("*UCSF*"), United States of America (*"USA"*).

2. He has an Integrative Oncology consultation practice at the UCSF Osher Center for Integrative Medicine.

3. He received an A.B. in Molecular Biology from Brown University in 1972 and graduated from the Stanford University School of Medicine in 1977.

4. After completing an Internal Medicine residency at the Kaiser Foundation Hospital in San Francisco, he became a fellow in Haematology-Oncology at the Cancer Research Institute of the University of California, San Francisco in 1980.

5. He was one of the original clinicians/investigators to recognize and define many early AIDS-related conditions. He has long been interested in clinical trials of complementary and alternative medicine interventions for HIV/AIDS and cancer, including evaluations of medicinal cannabis.

6. In 1997, he received funding from the (American) National Institute on Drug Abuse ("*NIDA*") to conduct clinical trials of the short-term safety of cannabinoids (chemical compounds derived from cannabis) in HIV infection. Subsequently, he was granted funds by the University of California Center for Medicinal Cannabis Research to continue studies of the medicinal efficacy of cannabis in a number of clinical conditions.

7. He completed a placebo-controlled study of smoked cannabis in patients with painful HIV-related peripheral neuropathy, as well as a study evaluating vaporization as a smokeless delivery system for medicinal cannabis use. He conducted a NIDA-funded trial, investigating the possible pharmacokinetic interaction between vaporized cannabis and opioid analgesics in patients with chronic pain.

8. He is now conducting a trial funded by the (American) National Institutes of Health ("*NIH*"), investigating vaporized cannabis in patients with Sickle Cell disease.

9. He co-authored the chapter on *"Cannabinoids and Cancer"* in the Oxford University Press **Integrative Oncology** text, which he co-edited with Andrew Weil.

10. He co-edits the National Cancer Institute's (*"NCI"*) Physician Data Query (*"PDQ"*) Complementary and Alternative Medicine (*"CAM"*) Cannabinoids and Cancer website.

11. The expert is a scientific advisor to a number of cannabinoid-based pharmaceutical companies.

12. The expert is a member of the United States' *"National Academies of Science, Engineering and Medicine's Committee to evaluate The Health Effects of Marijuana"*.

TAKE NOTICE FURTHER that a summary of the expert's opinions, and his reasons, therefor, are set out hereunder.

1. In order to express the opinions and provide the reasons set out hereunder, the expert:

    1.1. either conducted and/or participated in, *inter alia,* the following studies and/or published/authored, *inter alia*, the following (in many instances) peer-reviewed and (always) scientifically-credible research papers (which have been annexed hereto as annexures **"B"** to **"K"** and which are incorporated herein by reference and attachment):

        1.1.1. Journal article titled *"Medicinal Cannabis: Rational guidelines for dosing"* authored by, *inter alia*, the expert (as "DI Abrams"), as appears in IDrugs Journal, Issue 7 (item No 3 in Plaintiff's Discovery Affidavit dated **6 April 2016**);

        1.1.2. Journal Article titled *"Short-term effects of Cannabinoids in patients with HIV-1 Infection: a Randomized, Placebo-controlled Clinical trial"* authored by, *inter alia*, the expert, as appears in Annals of Internal Medicine Journal, volume 139 (item 6 in Plaintiff's Discovery affidavit dated **6 April 2016**);

        1.1.3. Journal Article titled *"Cannabis in Painful HIV-associated sensory neuropathy, a randomized placebo-controlled trial"* authored by,

inter alia, the expert, as appears in Neurology Journal, Issue 68 (item 7 in Plaintiff's Discovery affidavit dated **6 April 2016**);

1.1.4. Journal Article titled *"Vaporization as a smokeless Cannabis Delivery System: A Pilot Study"* authored by, *inter alia*, the expert, as appears in the Clinical Pharmacology and Therapeutics Journal (item 8 in Plaintiff's Discovery affidavit dated **6 April 2016**);

1.1.5. Journal Article titled *"Short Term Effects of Cannabinoids on immune phenotype and function in HIV-1 infected patients"* authored by, *inter alia*, the expert, as appears in The Journal of Clinical Pharmacology, Issue 42 (item 11 in Plaintiff's Discovery affidavit dated **6 April 2016**);

1.1.6. Journal Article titled *"Cannabinoid-Opioid Interaction in Chronic Pain"* authored by, *inter alia*, the expert, as appears in Clinical Pharmacology and Therapeutics Journal (item 12 in Plaintiff's Discovery affidavit dated **6 April 2016**);

1.1.7. Journal article titled *"Cannabis in Cancer care"* authored by, *inter alia*, the expert, as appears in Clinical Pharmacology and Therapeutics Journal (item 20 in Plaintiff's Discovery affidavit dated **6 April 2016**);

1.1.8. Journal article titled "*How an expert approaches it – Using Medical Cannabis in an Oncology Practice*", authored by the expert, as appears in The Oncology Journal (to be included in the Plaintiffs' Supplementary Discovery Affidavit);

1.1.9. Article titled "*Integrating cannabis into clinical cancer care*" authored by the expert, as appears in Current Oncology, March 2016 (to be included in the Plaintiffs' Supplementary Discovery Affidavit); and

1.1.10. Journal article titled "*Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data*", authored by, *inter alia*, the expert, as appears in The Journal of Pain (2015 Dec 31;16(12):1221-32).

1.2. as a medical doctor and experienced specialist, has recommended cannabis and/or its derivatives to patients for a variety of ailments and in order to treat many conditions for many decades, having observed and documented the effects thereof;

1.3. has had regard to, *inter alia*:

1.3.1. the scientifically-valid observations and conclusions made by him during the course of the aforesaid studies, papers and experience in-the-field;

1.3.2. the scientifically-valid observations and conclusions made by him in reading other studies and papers (as have been, or will be, discovered in this litigation and referred to by the expert in evidence);

1.3.3. the pleadings delivered in the above matter, including any and all requests for further particulars and responses thereto (as at date hereof); and

1.3.4. the First to Seventh Defendants' Notice in terms of Rule 36(9)(a) and (b) in respect of David Bayever, that was delivered on or about **25 January 2016**.

2. A summary of the expert's opinions (incorporating limited reasons therefore, but which are expanded upon in the annexures hereto) follows.

3. **NOTICE** is hereby given that this summary may be required to be supplemented, within the timeframes permissible in terms of the Uniform Rules of Court, as the expert (being on the forefront of the relevant science) becomes possessed of new/updated/supporting/contradictory evidence and/or research material.

3.1. **Cannabis and HIV**

3.1.1. Smoked and oral cannabinoids do not seem to be unsafe when used by people with human immunodeficiency virus ("*HIV*")

infection with respect to HIV ribonucleic acid ("*RNA*") levels, CD4 and CD8 cell counts, or protease inhibitor levels over a 21-day treatment.

3.1.2. In some instances, patients with HIV and/or AIDS were shown to gain more weight than placebo groups when orally ingesting, or smoking, cannabis or delta-9-THC as a complementary treatment.

3.1.3. Certainly, short-term use of cannabis by patients with HIV and/or AIDS does not appear to increase their viral load, when consumed in conjunction with a stable antiretroviral regimen.

3.1.4. Additionally, short-term cannabis usage does not appear to compromise the immune system, which was a widely-reported concern amongst clinical physicians. Specifically, the expert's study revealed no evidence of detrimental effects of cannabinoids on any of the immune parameters measured.

3.1.5. This allows for the conclusion that those who experience and/or report symptom management associated with their cannabis consumption are not putting themselves at short-term risk by so consuming cannabis, when one has regard to the desire to maintain, or keep down, or eliminate, viral loads in patients with HIV and/or AIDS.

3.1.6. Cannabis has been shown to assist in the management of painful HIV-associated sensory neuropathy.

3.2. **<u>Cannabis and Chronic Pain</u>**

3.2.1. The use of cannabis has been shown, and widely reported, to reduce pain and/or general pain, including, but not limited to, the pain caused by diabetes, rheumatoid arthritis, and fibromyalgia.

3.2.2. When utilised alongside traditional pharmaceutical pain medication (opioids, specifically stable-release morphine or oxycodone),

vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels.

3.2.3. The combination may allow for opioid treatment at lower doses, with fewer side effects.

3.2.4. Jurisdictions that have legalised, or decriminalised, cannabis use and possession have seen statistically-significant drops in deaths and complications associated with overdosing on traditional (opioid-based) pain medications.

3.3. Cannabis and Cancer

3.3.1. Cannabinoids, the active components of cannabis, mimic the effects of the endogenous cannabinoids (*"endocannabinoids"*), activating specific cannabinoid receptors, particularly CB1 found predominantly in the central nervous system and CB2 found predominantly in cells involved with immune function.

3.3.2. Delta-9-tetrahydrocannabinol, the main psychoactive cannabinoid in the plant, has been available as a prescription medication approved for the treatment of chemotherapy-induced nausea and vomiting and anorexia associated with the AIDS wasting syndrome.

3.3.3. Cannabinoids may be of benefit in the treatment of cancer-related pain, possibly synergistic with opioid analgesics.

3.3.4. In cancer patients, use of cannabis is able to, *inter alia*:

3.3.4.1. reduce nausea and vomiting, especially insofar as same is experienced by patients undergoing chemotherapy;

3.3.4.2. stimulate appetite;

3.3.4.3. reduce pain;

3.3.4.4. decrease anxiety and depression;

3.3.4.5. better sleep; and

3.3.4.6. (possibly) fight certain types of cancers themselves, as evidenced in preclinical (test tube and animal models) studies.

3.3.5. It is not unreasonable to infer that cannabis does not increase (and **may** decrease) the risk of healthy individuals developing certain types of cancer.

3.3.6. Cannabinoids have a favourable drug safety profile, but their medical use and medicinal properties are predominantly limited by their psychoactive effects and their limited bioavailability.

3.4. **Cannabis and Other Medical Ailments**

3.4.1. Albeit that many/most scientific studies focus on the pharmaceutical derivatives of cannabis (and not on the use/ingestion of the cannabis plant *per se*), there is reason to opine (*inter alia,* because of a limited number of scientific studies and because a number of US states allow cannabis to be used medicinally for the following) that cannabis is effective in treating the conditions of, and/or symptoms associated with, *inter alia* the following:

3.4.1.1. attention deficit disorder or attention deficit hyperactivity disorder;

3.4.1.2. alcoholism;

3.4.1.3. Alzheimer's;

3.4.1.4. arthritis;

3.4.1.5. anxiety;

3.4.1.6. crohns disease;

3.4.1.7. epilepsy;

3.4.1.8. heart disease and/or cardiovascular problems;

3.4.1.9. hepatitis C;

3.4.1.10. spasticity;

3.4.1.11. bladder dysfunction;

3.4.1.12. Tourette's syndrome;

3.4.1.13. insomnia;

3.4.1.14. multiple sclerosis;

3.4.1.15. osteoporosis; and

3.4.1.16. post-traumatic stress disorder.

3.4.2. Owing to his vast qualifications, expertise and experience, as aforesaid, the expert is well-placed to consider and analyse the scientific basis and available studies in respect of cannabis *vis-à-vis* the abovementioned ailments, and to provide a credible and reliable expert opinion thereon.

3.5. **Alleged Ill-Effects of Cannabis**

3.5.1. The expert is aware of the ill-effects allegedly associated with cannabis use, which include, *inter alia*:

3.5.1.1. schizophrenia;

3.5.1.2. a decrease in IQ and motivation;

3.5.1.3. respiratory disease;

3.5.1.4. cancer;

3.5.1.5. dependency;

3.5.1.6. addiction;

3.5.1.7. dizziness;

3.5.1.8. dry mouth;

3.5.1.9. nausea/vomiting;

3.5.1.10. fatigue;

3.5.1.11. reduced co-ordination;

3.5.1.12. ataxia;

3.5.1.13. euphoria;

3.5.1.14. disorientation and confusion;

3.5.1.15. loss of balance;

3.5.1.16. hallucinations;

3.5.1.17. anxiety; and

3.5.1.18. coughing.

3.5.2. However, the expert is of the opinion that some, if not many, of these alleged ill-effects:

3.5.2.1. are, to some extent, exaggerated by politicians and journalists, who do not understand the science underlying them;

3.5.2.2. lack any, or any significant, credible scientific basis (even after many decades of research providing the potential for scientific conclusion in this regard);

3.5.2.3. being relatively minor in extent, are not, when assessed, counterbalanced by the potential benefits of cannabis (and/or its derivatives) use;

3.5.2.4. can often be managed by a *"start low, go slow"* approach; and

3.5.2.5. in any event, fall well within the parameters of the (scientifically-established) harms of non-prohibited substances, such as tobacco, alcohol and opioids.

3.6. **General Observations**

3.6.1. Cannabis has been consumed by people for thousands of years, both recreationally and medicinally.

3.6.2. It was first introduced into Western medicine in 1842, whereafter it was successfully used all over the modern world for the treatment of numerous conditions.

3.6.3. In the early 1900s, medicines that were indicated for each of cannabis' purported activities were introduced into the Western armamentarium, making cannabis' use less widespread.

3.6.4. In 1942, cannabis was removed from the United States Pharmacopoeia. In 1970, with the initiation of the Controlled Substances Act, cannabis was classified as a Schedule I drug in the USA.

3.6.5. This rejection of cannabis was more politically-motivated than scientifically-motivated.

3.6.6. Where both Schedule I and Schedule II substances, in America, have a high potential for abuse, Schedule I drugs are distinguished by having no accepted medical use. Other Schedule I substances include heroin, lysergic acid diethylamide ("*LSD*"), mescaline, methylqualone, and, most recently, gammahydroxybutyrate ("*GHB*").

3.6.7. Despite numerous, far-reaching efforts to change the scheduling of cannabis, federally, in the United States, it remains a Schedule I substance at this time.

3.6.8. There are numerous methods of ingesting cannabis, some methods being safer than others. These include, *inter alia*:

3.6.8.1. smoking dried cannabis;

3.6.8.2. vaporizing dried cannabis;

3.6.8.3. smoking cannabis-extract wax or oil;

3.6.8.4. eating cannabis-extract wax or oil;

3.6.8.5. eating goods infused with dried cannabis; and

3.6.8.6. administering cannabis oil rectally.

3.6.9. It is virtually impossible to die from a cannabis overdose when ingested in the manner and quantities considered *"usual"* (or, for that matter, possible).

3.6.10. Although cannabinoids are considered by some to be addictive drugs, their addictive potential is considerably lower than other prescribed agents or substances of abuse, with the risk being much lower than that of nicotine, heroin, cocaine, and alcohol (amongst other substances).

3.6.11. Most drug users begin with alcohol and nicotine before cannabis. Hence, cannabis would very rarely be the first *"gateway"* drug and there is no conclusive evidence that the drug effects of cannabis are causally linked to the subsequent abuse of other illicit drugs.

3.6.12. In this regard, the classification of cannabis as *"illicit"*, while alcohol and nicotine are classified as *"acceptable"*, is artificial, irrational and unscientific.

3.6.13. Most physicians currently practising medicine were schooled during the "*cannabis prohibition era*" (as still applies in most parts of the world, including in South Africa) and have little-to-no knowledge of the biological actions of (endo)cannabinoids and the medicinal qualities of cannabis. Much of the discussion is dominated by addiction medicine specialists, who have a skewed view of the health consequences of cannabis use, specifically by virtue of their specialty.

3.6.14. Data from gold-standard prospective, randomized, controlled, clinical trials is virtually non-existent. One reason for this is that the only legal source of cannabis for research in the United States is the National Institute on Drug Abuse ("*NIDA*"). NIDA has a congressional mandate to study substances of abuse *only* as substances of abuse and not as therapeutic interventions. Similar restrictions apply in other countries, including South Africa.

3.6.15. Patients are often reluctant to try cannabis as a medicine, because of the stigma that they associate with its use, or for fear of addiction, despite the fact that the addictive potential is extremely low.

3.6.16. The expert does not consider euphoria caused by cannabis usage in his patients to be an adverse or undesirable event by any means. Cannabis is a single medicine that he would readily recommend to assist with, *inter alia,* nausea, anorexia, insomnia, depression, and pain, rather than prescribing five or six pharmaceuticals that may

interact with each other or the patient's chemotherapy. He considers it an attractive option for his patients.

3.6.17. Given all of the above, rational legal, legislative and medicinal guidelines are required for cannabis usage. This can never be achieved whilst users, doctors and researchers face the threat of criminal prosecution.

3.7. **Conclusions**

3.7.1. Given, *inter alia*, all of the above:

in respect of the First and Second Plaintiffs (and people similarly placed):

3.7.1.1. the expert does not consider it a rational application of the law to continue to criminalise the use and possession of cannabis, whilst allowing people to use and possess more harmful substances, such as tobacco and alcohol;

3.7.1.2. the (proven) medicinal harms of cannabis use (which are relatively minor) are far outweighed by the detrimental effects of criminal prohibition (including the stress of getting caught, facing prosecution, and going to prison, where one is exposed to harder drugs, hardened criminals and possibly life-threatening diseases);

in respect of the Third Plaintiff (and people similarly placed):

3.7.1.3. moreover, cannabis is a medicinally-beneficial substance that can be used for the treatment of a variety of medical conditions and ailments;

3.7.1.4. in the circumstances, it appears to be a violation of the rights of the poor (or anyone, for that matter) to (under threat of criminal prosecution) deprive them of access to what is a relatively cheap and effective alternative to

many unaffordable pharmaceutical equivalents (potential ill-effects considered);

in respect of all Plaintiffs (and people similarly placed):

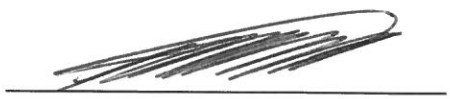
3.7.1.5. it appears unreasonable and irrational to deprive people of access to, at worst, a relatively low-harm vice and, at best, a substance that constitutes preventative medicine;

in general:

3.7.1.6. education around, and further scientific research into, cannabis (as are taboo under any prohibitive regime) can be considered very positive outcomes; and

3.7.1.7. therefore, the expert opines that full legalisation, or decriminalisation, of the use and possession of cannabis constitutes an effective way to manage a substance that has been demonstrated to not present the (full extent of the) harms espoused by prohibitionists.

Dated and signed at Melrose Arch on the 30th day of September 2016.



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TO: THE REGISTRAR OF THE ABOVE
HONOURABLE COURT
PRETORIA

AND TO: **THE STATE ATTORNEY**
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Received on this ____ day of _____ **2016**

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EDUCATION:

1968-1972	Brown University, Providence, Rhode Island	A.B.	Molecular Biology
1972-1977	Stanford University School of Medicine	M.D.	Medicine
1977-1980	Kaiser Foundation Hospital San Francisco	Resident	Internal Medicine
1980-1983	University of California San Francisco	Fellow	Hematology-Oncology
2003-2004	University of Arizona	Fellow	Integrative Medicine

LICENSES, CERTIFICATION:

1978	Medical licensure, California G36948
1980	Diplomate, American Board of Internal Medicine
1983	Diplomate, Subspecialty of Medical Oncology

PRINCIPAL POSITIONS HELD:

1982-83	UCSF	Assistant Research Physician	Cancer Research Institute
1983-84	UCSF	Clinical Instructor	Medicine

1984-88	UCSF	Assistant Clinical Professor	Medicine
1988-92	UCSF	Associate Professor of Clinical Medicine	Medicine
1992-now	UCSF	Professor of Clinical Medicine	Medicine

OTHER POSITIONS HELD CONCURRENTLY:

1983-1996	San Francisco General Hospital AIDS Program	Assistant Director
1996-2003	San Francisco General Hospital Positive Health Program	Heme-Onc Section Head
2003-now	San Francisco General Hospital Heme-Oncology Division	Chief
2006-2008	UCSF Osher Center for Integrative Medicine	Director of Clinical Programs

HONORS AND AWARDS:

1968-72	National Merit Scholar, Brown University
1969	Ratcliffe Hicks Award & Francis Wayland Scholar, Brown University
1972	Sigma Nu, Brown University
1973-77	California State Fellow, Stanford University School of Medicine
1986-89	American Cancer Society Career Development Award, UCSF/SFGH
1988	Community Service Award, Bay Area Physicians for Human Rights
1990	Achievement Award, American Association of Physicians for Human Rights
1990	Assistant Secretary of Health's Award for Outstanding Accomplishment
1991	Assistant Secretary of Health's Award for Outstanding Accomplishment, Community Consortium
1994, 04, 05	UCSF Kaiser Award for Excellence in Teaching, Nominee
1994, 97, 98	UCSF Teaching Award for Excellence in Small Group Instruction, Nominee
1997	Project Inform Certificate of Appreciation and Outstanding Achievement
2000	American Foundation for AIDS Research Award of Courage
2000	International Association of Physicians in AIDS CARE (IAPAC) Heroes in Medicine Award
2000	Stanford University School of Medicine Top 40 Alumni of Past 40 years
2000	Brown University Top 100 Distinguished Alumni of the Century
2002	Chancellor's Award for GLBT Leadership
2002	George S. Sarlo Award for Excellence in Mentoring
2007	International Association for Cannabis as Medicine Award for Clinical Research
2009	National Organization for the Reform of Marijuana Laws Lester Grinspoon Award
2015	Patients Out of Time Lifetime Achievement in Cannabis Medicine
2015	2015 Lesbian, Gay. Bisexual & Transgender (LGBT) Leadership Award from the California Legislative LGBT Caucus
2015	Newsweek Magazine 2015 Top Cancer Doctors

PROFESSIONAL ORGANIZATIONS:

Memberships

1978-Present	American College of Physicians (Fellow 1987)
1983-Present	Gay and Lesbian Medical Association (Treasurer 1995- 98; President 1999-00)
1984-1988	American Society of Hematology

1985-Present	American Society of Clinical Oncology
1987-Present	California Medical Association
1987-Present	San Francisco Medical Society
1988-2006	International AIDS Society
1989-Present	American Medical Association
1999-Present	Association of American Physicians
2004-Present	Society for Integrative Oncology

Service to Professional Organizations

1995-1998	Gay and Lesbian Medical Association	Treasurer
1999-2000	Gay and Lesbian Medical Association	President
2005-2006	American Society Clinical Oncology	Chairman, Continuing Medical Education Committee
2007-2009	Amercian Society Clinical Oncology	Member, Educational Products Subcommittee
2005-Present	Society for Integrative Oncology	Scientific Program Committee Chair 2006-8, Secretary/Treasurer 2007-8, Vice-President 2008-9, President 2010
2011-Present	California Medical Association	Technical Advisory Committee: Medical Marijuana
2011-Present	American Board of Integrative Medicine	Founding Board Member
2013-Present	American Botanical Council	Advisory Board

SERVICE TO PROFESSIONAL PUBLICATIONS

EDITORIAL BOARDS:

AmFAR AIDS/HIV Treatment Directory, Medical Editor (1986-1996)
AIDS: An International Bimonthly Journal, Gower Academic Journals
AIDS Knowledgebase, BRS
HIV InSite
Journal of AIDS
AIDS Section, Life Sciences
AIDS and STDs
Oncology
Journal of the Gay and Lesbian Medical Association
Actualizaciones en SIDA (Argentina), Foreign Advisory Committee
Atualizacao em AIDS (Brazil), Foreign Advisory Committee
The United States Pharmacopeial Convention
International Association for Cannabis as Medicine (IACM) Journal
Integrative Medicine Insights
Journal of the Society of Integrative Oncology (Associate Editor)
Chinese Medicine
Integrative Cancer Therapies
Journal of Supportive Oncology
National Cancer Institute Physician's Data Query Complementary and Alternative Medicine (NCI PDQ CAM)

INVITED JOURNAL REVIEWS:

American Journal of Medicine
Annals of Internal Medicine
Archives of Internal Medicine
Blood
Cancer Research
Community Oncology
Gastroenterology
Integrative Cancer Therapies
Journal of the American Medical Association
Journal of Clinical Immunology
Journal of Clinical Investigation
Journal of Infectious Diseases
Journal of Clinical Oncology
Journal of Laboratory and Clinical Medicine
Journal of the Society of Integrative Oncology
Lancet
New England Journal of Medicine
Proceedings of the National Academy of Sciences
Science
Western Journal of Medicine

GOVERNMENT and OTHER PROFESSIONAL SERVICE

1989-2006	NIH/NIAID/Community Programs on Clinical Research in AIDS (CPCRA)
	Chair Antiviral Research and/or Science Planning Committee, 1990-1999
	Chair Publications and Presentations Subcommittee, 2000-present
1990-93	Food and Drug Administration: Antiviral Advisory Committee, Charter Member
1996-99	Food and Drug Administration: Oncology Drug Advisory Committee, Consultant
1999-present	Health Canada Ad Hoc Grant Reviewer
1999-present	National Center for Complementary and Alternative Medicine Ad Hoc Grant Reviewer
2005	National Center for Complementary and Alternative Medicine Study Section Chair
2005-06	Consultant to Columbia University International Center for AIDS Care and Treatment Programs Site visits to Dar Es Salaam, Tanzania (12/05) and Maputo, Mozambique (5/06)
2009-present	National Cancer Institute PDQ Editorial Board
2013-present	American Botanical Council: Advisory Board

UNIVERSITY SERVICE

SYSTEM-WIDE

1986- 2006	Ad Hoc Peer Grant Reviews for Universitywide AIDS Research Program
2000-2001	Co-Director University of California Center for Medicinal Cannabis Research

UCSF CAMPUS-WIDE

2003- 2006	UCSF Helen Diller Family Comprehensive Cancer Center Minority Task Force
2003- 2010	UCSF Helen Diller Family Comprehensive Cancer Center Executive Committee
2004- present	UCSF Helen Diller Family Comprehensive Cancer Center Developing Program in Symptom Management, Palliative Care and Survivorship, Co-Chair
2007-present	Resource Allocation Program Cancer Review Committee
2008-present	UCSF Helen Diller Family Comprehensive Cancer Center Cancer Committee member

SCHOOL OF MEDICINE

1999- 2006	Promotions Subcommittee, Committee on Promotions and Appointments
2003-present	Site Director, UCSF Hematology-Oncology Fellowship Program
2004-2005	Associate Director, UCSF Hematology-Oncology Fellowship Program

DEPARTMENTAL SERVICE

1983- present	Cancer Committee San Francisco General Hospital	Co-Chair 2004-
2000- present	General Clinical Research Center SFGH	GCRC Advisory Committee

PUBLIC SEVICE

1983-84	Scientific Advisory Committee, AIDS Foundation, San Francisco
1984	AIDS Advisory Committee, San Francisco Department of Public Health
1985-2006	San Francisco County Community Consortium, Chairman
1985	International Program Committee, Second International Conference on AIDS, Paris, France
1986	World Health Organization - Program on AIDS, Consultant
1987-90	Organizing Committee, Sixth International Conference on AIDS, San Francisco, California, 1990
1987-92	Scientific Advisory Committee, AmFAR (American Foundation for AIDS Research)
1987-89	West Bay Hospital Conference AIDS Task Force
1987-88	Chancellor's Technical Advisory Committee on AIDS, UCSF, Chairman
1988	UCSF AIDS Coordinating Council
1988	Programme Committee, Fifth International Conference of AIDS, Montreal, Canada, 1989
1988	Ambulatory Care Committee, AIDS Office, San Francisco Department of Public Health
1989-90	UCSF 125th Anniversary Committee
1989	American Medical Association Diagnostic & Therapeutic Technology Assessment Reference Panel
1989	Center for AIDS Research (UCSF) Executive Committee
1989	Blood Borne Pathogen Committee, SFGH
1990-94	Protocol Evaluation Subcommittee, AIDS Clinical Trials Group, NIAID
1990-92	Board of Directors, American Cancer Society, San Francisco Unit
1990-98	Continuing Medical Education Advisory Committee, UCSF
1991	Keystone Center National Policy Dialogue on Expanded Access
1991	DPHS - State of California, AIDS Drug Program Advisory Committee
1992-95	San Francisco General Hospital Executive Committee, At Large Member
1992	National Human Subjects Protection Review Panel, Ad Hoc Consultant

1993	American Association of Physicians for Human Rights, Executive Board
1993	Noah's Ark-Red Cross Foundation International Advisory Committee
1993	Program Committee, Tenth International Conference on AIDS
1995	International Scientific Committee, 11th International Conference on AIDS
1996	Chancellor's Advisory Board on AIDS and Other Infectious Diseases
1996-2000	Chancellor's Advisory Committee on Gay, Lesbian and Bisexual Issues
1996-99	Transfusion Committee, San Francisco General Hospital
1997	Medical Marijuana Technical Advisory Committee, California Medical Association
1998	Alternative Therapies Technical Advisory Committee, California Medical Association
1998-2002	AIDS Research Institute Executive Committee, At Large Member
1998-	The Center for Attitudinal Healing, Advisory Board
2003-	National Center for Complementary and Alternative Medicine, Ad Hoc Grant Reviews
2003-	Health Canada Ad Hoc Grant Reviewer
2003-	Continuing Medical Education Committee, American Society of Clinical Oncology (Chair 05-06)
2005	National Center for Complementary and Alternative Medicine Study Section Chair, March
2007-2010	UC Berkeley Camp Kesem (Camp for children of cancer patients); Board of Directors
2008-	The Weil Foundation; Board of Directors
2011	Ceres Community Project Ambassador Council

TEACHING AWARDS AND NOMINATIONS:

1994, 04, 05	UCSF Kaiser Award for Excellence in Teaching, Nominee
1994, 97, 98	UCSF Teaching Award for Excellence in Small Group Instruction, Nominee
2002	George S. Sarlo Award for Excellence in Mentoring

RESEARCH AND CREATIVE ACTIVITIES

RESEARCH AWARDS AND GRANTS

CURRENT

OU1HL117664 (Co-investigator)	08/01/2013 – 05/31/2016
NIH/NHLBI/University of Minnesota subcontract	$210,292 direct/yr 1
Cannabinoid-based therapy and approaches to quantify pain in sickle-cell disease	$738,006 direct/yrs 1 - 3
UM1CA181255 (Co-investigator)	09/23/2013-08/31/2018
NIH/NCI	$3,169,869 direct/yr 1
AIDS and Cancer Specimen Resource (ACSR)	$16,549,803 direct/yrs 1 - 5
U01CA121947 (Co-investigator)	09/01/10 – 08/31/15
NCI/NIH/ Subcontract with EMMES Corporation	$97,851 direct/yr 4
AIDS Malignancies Consortium (AMC)	$531,144 directyrs 1 - 5

PAST

UO1 CA66529 (Co-Investigator)	08/01/98 – 08/31/13
NIH/NCI	$808,650 direct/yr 14
West Coast AIDS and Cancer Specimen Resource Consortium	$4,234,611 direct/yrs 14 - 18
R01CA134234 (Co-Investigator)	09/24/08 – 07/31/12
NIH	$12,700 direct/yr 1
Prognostic Markers for HIV-Positive Diffuse Large B-Cell Lymphoma (DLBCL)	$33,500 direct/yrs 1 - 5
1 U01 AI068641-01 (Co-Investigator)	07/01/06 – 05/31/11
NIH/NIAID	$146,180 direct/yr 1
International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)	$776,089 directs/yrs 1 - 5
P30 CA82103 (Co-Investigator)	08/05/99 - 05/31/12
NIH/NCI	$4,924,500 direct/yr 10
Cancer Center Support Grant	
R21 DA020831-01 (PI)	04/01/06 – 03/31/09
NIDA	$125,000 direct/yr 1
Opioid and Cannabinoid Pharmacokinetic Interactions	$275,000 direct/yrs 1 - 2
P01 AT002024 (Co-Investigator)	
NIH/NCCAM	09/30/04 - 06/30/09
Mindfulness-Based Stress Reduction (MBSR)	$283,726 direct/yr 1
Stress Arousal and Immune Response in Early HIV	$1,064,433 direct/yrs 1 - 5
#20070658 (Co-Investigator)	05/01/08 - 04/30/09
Mount Zion Health Fund	$34,874 direct/yr 1
Yoga Breathing for Cancer Chemotherapy Symptom Management	
R01 CA119903 (Co-Investigator)	09/30/05 - 07/31/08
NIH-NCI	$407,261 direct/yr 1
Antiretroviral Therapy of AIDS-Related Kaposi's Sarcoma in Africa	$1,729,460 direct/yrs 1 - 5
U01 AI42169 (PI)	09/30/89 - 03/31/07
NIH/NIAID	$846,979 direct/yr 10
CPCRA:Community Programs for Clinical Research on AIDS	$17,000,000 directs/yrs 1 – 16
U01 AI46957-03 (PI)	08/24/01 - 07/31/06
NIH/NIAID/University of Minnesota	$116,012 direct/yr 1
Subcontract	$656,332 direct/yrs 1 - 7
San Francisco National Clinical Trial Center, ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial)	
R01 DA/MH 11607 (PI)	10/01/97 – 9/30/00
NIH/NIDA/NIMH	$304,839 direct/yr 1
Short-Term Effects of Cannabinoids in Patients with HIV-1 Infection	$809,394 direct/yrs 1 - 3
R01 AT00485 (Co-Investigator)	07/01/00 - 04/30/03
NIH/NCCAM/CPMC	$41,153 direct/yr 1
Study of the Effects on Distant Healing Efforts by "Healers" and by Nurses in Advanced AIDS Patients	$86,908 direct/yrs 1 - 3
R01 AT00512 (PI)	07/01/00 - 04/30/03
NIH/NCCAM	$256,172 direct/yr 1

Dehydroepiandrosterone (DHEA) Effects on HIV-1 Replication and Host Immunity: A Randomized, Placebo-Controlled Pilot Study	$789,589 direct/yrs 1 - 3
C00-SF-101 (PI)	09/01/01 - 08/31/04
CMCR, UC San Diego	$315,316/direct yr 1
Marijuana for Treatment of HIV-related Peripheral Neuropathy	$955,971 direct/yrs 1 - 3
C00-SF-108 (PI)	05/01/03 - 04/30/04
CMCR, UC San Diego	$250,368 direct/yr 1
Marijuana in Combination with Opioids for Cancer Pain	
CRO0-SF-041 (PI)	07/01/00 - 06/30/02
UARP	$90,966 direct/yr 1
Clinica Guidelines and Clinical Effectiveness in HIV Care	$183,488 direct/yrs 1 - 2
CRO2-SF-610 (PI)	10/01/02 - 09/30/04
UARP	$89,875 direct/yr 1
When to Change Anti-HIV Therapy: Testing Guidelines	$182,117 direct/yrs 1 - 2
C03-SF-115 (PI)	
CMCR, UC San Diego	07/01/04 – 06/31/05
Vaporization as a “Smokeless” Cannabis Delivery System	$137,488 direct/yr 1
R21 AT001782 (PI)	09/15/03 – 05/31/06
NCCAM	$125,000 direct/ yr 1
Antihyperlipidemic Effects of Oyster Mushrooms	$250,000 direct/yrs 1 - 2

PEER REVIEWED PUBLICATIONS

JOURNAL ARTICLES:

1. **Abrams DI,** Dawson C, O'Donnell J, and Char D. Retinal findings in opportunistic infections of homosexual males. Audio J Rev Ophthalmo 8: August, 1982.
2. Ziegler JL, Wagner G, Greenspan JS, **Abrams DI**, et al. Diffuse undifferentiated non-Hodgkin's lymphoma among homosexual males - United States. MMWR 31:277-279, 1982.
3. Drew WL, Miner RC, Ziegler JL, Gullett JH, **Abrams DI**, Conant MA, Huang ES, Groundwater JR, Volberding PA, and Mintz L. Cytomegalovirus and Kaposi's sarcoma in young homosexual men. Lancet ii:125-127, 1982.
4. Olson J, Feinberg I, Silverman S, **Abrams DI**, and Greenspan J. Serum vitamin B_{12}, folate, and iron levels in recurrent aphthous ulceration. Oral Surg, Oral Med, Oral Pathol 54:517-520, 1982.
5. Ammann A, **Abrams DI**, Conant M, Chudwin D, Cowan M, Volberding PA, Lewis B, and Casavant C. Acquired immune dysfunction in homosexual men: Immunologic profiles. Clin Immunopathol 27:315-325, 1983.
6. Moss A, Bacchetti P, Gorman M, Dritz S, Conant M, **Abrams DI**, Volberding P, and Ziegler J. AIDS in the "gay" areas of San Francisco. Lancet i:923-924, 1983.
7. Jaffe HS, **Abrams DI**, Golden JA, Ammann AJ, and Lewis BJ. Complications of trimethoprim sulfamethoxazole in the treatment of AIDS associated ***Pneumocystis carinii*** pneumonia in homosexual men. Lancet ii:1109, 1983.
8. Spector DH, Shaw SB, Hock LJ, **Abrams DI**, Mitsuyasu RT and Gottlieb ME. Association of human cytomegalovirus with Kaposi's sarcoma. UCLA Symposia on molecular and cellular biology, 1983.
9. **Abrams DI**, Chinn E, Volberding P, Lewis B, Conant M and Townsend R. Hematologic manifestations of Kaposi's sarcoma in homosexual men. Am J Clin Pathol 81:13-18, 1984.

10. Ammann AJ, Schiffman G, **Abrams DI**, Volberding P and Conant M. Acquired B-cell immunodeficiency disease. J Am Med Assoc 251:1447-1449, 1984.

11. Valone FH, Payan DG, **Abrams DI** and Goetzl EJ. Defective polymorphonuclear leukocyte chemotaxis in homosexual males with persistent lymph node syndrome. J Inf Dis 150:267-271, 1984.

12. Moon KL, Federle MP, **Abrams DI**, Volberding PA and Lewis BJ. Kaposi's sarcoma and lymphadenopathy syndrome: Limitations of the abdominal CT in acquired immunodeficiency syndrome. Radiology 150:479-83, 1984.

13. Ziegler JL, Beckstead JA, Volberding PA, **Abrams DI**, Levine AM, Lukes RJ, et al. Non-Hodgkin's lymphoma in 90 homosexual men: Relationship to generalized lymphadenopathy and acquired immunodeficiency syndrome (AIDS). N Engl J Med 311:565-570, 1984.

14. Stern RG, Gamsu G, Golden JA, Hirji M, Webb WR and **Abrams DI**. Intrathoracic adenopathy in AIDS and the diffuse, persistent lymphadenopathy syndrome: Diagnostic and clinical implications. Am J Roentgenol 142:689-92, 1984.

15. **Abrams DI**, Lewis BJ, Beckstead JH, Casavant C and Drew WL. Persistent diffuse lymphadenopathy in homosexual men: Endpoint or prodrome? Ann Intern Med 100:801-808, 1984. Valone FH, Payan DG,

16. **Abrams DI** and Goetzl EJ. Indomethacin enhances the proliferation of mitogen-stimulated T-lymphocytes from homosexual men with reactive lymph node syndrome. J Clin Immunol 4(5):383-387, 1984.

17. **Abrams DI**, Lewis BJ and Volberding PA. Lymphadenopathy: Endpoint or Prodrome? Update of a 24-month prospective study. Ann NY Acad Sci 437-207-215, 1984.

18. Ziegler JL, Bragg K, **Abrams DI**, Beckstead J, Volberding PA, Baer D, Wilkinson L, Rosenbaum E, Grant K, Silverberg I, McGrath I. High grade non-Hodgkins lymphoma in patients with AIDS. Ann NY Acad Sci 437:412-419, 1984.

19. Moss AR, Bacchetti P, Osmond D, Dritz S, **Abrams DI**, Conant M and Volberding P. Incidence of the acquired immunodeficiency syndrome in San Francisco 1980-1983. J Inf Dis 152:152-161, 1985.

20. Volberding P and **Abrams DI**. Ethical issues elicited by clinical care and research in AIDS. In: AIDS: The Emerging Ethical Dilemmas. The Hastings Center Report 15(4):16-18, 1985.

21. Kiprov DD, Lippert R, Sandstrom E, Jones FR, Cohen RJ, **Abrams DI**, Busch DF. Acquired immunodeficiency syndrome (AIDS) - apheresis and operative risks. J Clin Apher 2:427-440, 1985.

22. Stricker RB, **Abrams DI**, Corash L, Shuman MA. Target platelet antigen in homosexual men with immune thrombocytopenia. New Engl J Med 313:1375-1380, 1985. (Revoked subsequently)

23. Lipkin I, Parry G, Kiprov D, **Abrams DI**. Inflammatory neuropathy in homosexual men with lymphadenopathy. Neurology 35(10):1479-1483, 1985.

24. **Abrams DI**, Kiprov DD, Goedert JJ, Sarngadharan MG, Gallo RC, Volberding PA. Antibodies to human T-lymphotropic virus type-III antibodies and development of acquired immunodeficiency syndrome in homosexual men presenting with immune thrombocytopenia. Ann Intern Med 104:47-50, 1985.

25. Greenspan JS, Greenspan D, Lennette ET, **Abrams DI**, Conant MA, Petersen V, Freese UK. Epstein-Barr virus replicates within the epithelial cells of oral "hairy" leukoplakia, an AIDS-associated lesion. N Engl J Med 313:1564-1571, 1985.

26. Bottles K, Cohen MB, Brodie H, Jeffreys RB, **Abrams DI**. Fine needle aspiration cytology of lymphadenopathy in homosexual males. Diagnostic Cytopathology 2:31-35, 1986.

27. Jeffrey RB, Nyberg DA, Bottles K, **Abrams DI**, Federle MP, Wall SW, Wing VW,Laing FC. Abdominal CT in acquired immunodeficiency syndrome. AJR 146:7-13, 1986.

28. Nyberg DA, Jeffrey RB, Federle MP, Bottles K, **Abrams DI**. AIDS-related lymphomas: Evaluation by abdominal CT. Radiology 159:59-63, 1986.

29. Bloom EJ, **Abrams DI**, Rodgers G. Lupus anticoagulant in the acquired immunodeficiency syndrome. JAMA 256:491-493, 1986.

30. Kiprov DD, Lippert R, Miller RG, Sandstrom E, Jones FR, Cohen RJ, **Abrams DI**, Busch DF. The use of plasmapheresis, lymphocytapheresis, and staph protein-A immunoadsorption as an immunomodulatory therapy in patients with AIDS and AIDS-related conditions. J Clin Apher 3:133-139, 1986.

31. **Abrams DI**, Kaplan LD, McGrath MS, Volberding PA. AIDS-related benign lymphadenopathy and malignant lymphoma: clinical aspects and virologic interactions. AIDS Res 2(Suppl 1):S131-S139, 1986.
32. Kaplan LD, Volberding PA, **Abrams DI**. Treatment of Kaposi's sarcoma in acquired immunodeficiency syndrome with an alternating vincristine-vinblastine regimen. Cancer Treat Rep 70:1121-1122, 1986.
33. Greenspan D, Greenspan JS, Hearst NG, Pan L-Z, Conant MA, **Abrams DI**, Hollander H, Levy JA. Relation of oral hairy leukoplakia to infection with human immunodeficiency virus and risk of developing AIDS. J Inf Dis 55:475-481, 1987.
34. Kiprov DD, Simpson DM, Pfaeffl WA, Romanick-Schmiedl S, **Abrams DI**, Miller RG. AIDS and apheresis procedures -therapeutic and safety considerations. Blood Purification 5:51-56, 1987.
35. Kaplan LD, Wolfe PR, Volberding PA, Feorino P, Levy JA, **Abrams DI**, Kiprov D, Wong R, Kaufman L, Gottlieb MS. Lack of response to suramin in patients with AIDS and AIDS-related complex. Am J Med 82:615-620, 1987.
36. Ayers MR, **Abrams DI**, Newell TG, Friedrich F. Performance of Individuals with AIDS on the Luria-Nebraska Neuropsychological Battery. Int J of Clin Neuropsych 9:101-105, 1987.
37. Ammann AJ, Palladino MA, Volberding P, **Abrams DI**, Martin NL, West R, Conant M. Tumor necrosis factors alpha and beta in acquired immunodeficiency syndrome and AIDS-related complex. J Clin Immunol 7(6):481-485, 1987.
38. Schneider PA, **Abrams DI**, Rayner AA, Hohn DC. Immunodeficiency associated thrombocytopenic purpura (IDTP): Response to splenectomy. Archives of Surgery 122:1175-1178, 1987.
39. Moran TA, Lovejoy N, Viele CA, Dodd MJ, **Abrams DI**. Informational needs of homosexual men diagnosed with AIDS or AIDS-related complex. Oncology Nursing Forum 15:311-314, 1988.
40. So YT, Holtzman, **Abrams DI**, Olney RK. Peripheral neuropathy associated with Acquired Immune Deficiency Syndrome (AIDS): Prevalence and clinical features from a population based survey. Archives of Neurology 45:945-948, 1988.
41. Moskovtiz B, Lane HC, Masur H, Lange M, England A, McKinley G, Volberding PA, **Abrams DI**, et al. HPA Cooperative Study Group. A clinical trial of tolerance of HPA-23 in patients with acquired immune deficiency syndrome (AIDS). Antimicrobial agents and chemotherapy 32: 1300-1303, 1988.
42. Kaplan LD, **Abrams DI**, Feigal E, McGrath MS, Kahn J, Neville P, Ziegler J, Volberding PA. AIDS associated non-Hodgkin's lymphoma in San Francisco. JAMA 261:719-724, 1989.
43. **Abrams DI**, Kuno S, Wong R, Jeffords K, Nash M, Molaghan JB, Gorter R, Ueno R. Oral Dextran sulfate (UA001) in the treatment of the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. Ann Intern Med 110:683-188, 1989.
44. Jacobson MA, **Abrams DI**, Volberding PA, Bachetti P, Wilber J, Chaisson R, Crowe S, Howard W, Moss A. Serum Beta-2 microglobulin decreases in patients with AIDS or ARC treated with azidothymidine. J Inf Dis 159:1029-1036, 1989.
45. Krowka JF, Stites DP, Jain S, Steimer KS, George-Nascimento L, Gyenes A, Barr PJ, Hollander H, Moss AR, Homsy JM, Levy JA, **Abrams DI**. Lymphocyte proliferative responses to human immunodeficiency virus antigens *in vitro*. JCI 83:1198-1203, 1989.
46. Leoung G, Feigal D, Montgomery AB, Corkery K, Wardlaw L, Adams M, Busch D, Gordon S, Jacobson M, Volberding P, **Abrams DI**, and the San Francisco County Community Consortium. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia. The San Francisco Community Prophylaxis Trial. NEJM 323:769-775, 1990.
47. **Abrams DI**. The relationship between Kaposi's Sarcoma and intestinal parasites among homosexual males in the United States. JAIDS 3(suppl.1):544-546, 1990.
48. Kaplan LD, **Abrams DI**, Sherwin SA, Kahn J, Volberding PA. A phase I/II study of recombinant tumor necrosis factor and recombinant interferon gamma in patients with AIDS-related complex. Biotech Ther 1(3)i-ii, 229-236, 1990.
49. Jacobson M, Bacchetti P, Kolokathis A, Chaisson R, Szabo S, Polsky B, Valainis G, Mildvan D, **Abrams DI**, Wilber J, Winger E, Hendricksen C, Moss A. Surrogate markers for survival in patients with AIDS and ARC treated with zidovudine. Brit Med J 302:73-8, 1990.

50. Scitovsky A, Cline MB, and **Abrams DI**. Effects of the use of AZT on the medical care costs of persons with AIDS in the first 12 months. JAIDS 3:904-912, 1990.

51. Greenspan D, Greenspan JS, Overby G, Hollander H, **Abrams DI**, MacPhail L, Borowsky C, Feigal DW. Risk factors for rapid progression from hairy leukoplakia to AIDS: a nested case control study. JAIDS 4:652-658, 1991.

52. Hersh EM, Brewton G, **Abrams DI**, Bartlett J, Galpin J, Gill P, et al. A randomized double-blind placebo-controlled multicenter study of sodium ditiocarb (diethyldithiocarbamate) therapy in patients with ARC and AIDS. JAMA 256:1538-1544, 1991.

53. Kaplan LD, Kahn JO, Crowe S, Northfelt D, Neville P, Grossberg H, **Abrams DI**, Tracey J, Mills J, Volberding P. Clinical and virologic effect of recombinant human granulocyte-macrophage colony-stimulating factor (rGM-CSF) in patients receiving chemotherapy for HIV-associated non-Hodgkin's lymphoma: results of a randomized trial. J.Clin.Oncol 9:929-940, 1991.

54. Northfelt DW, Mayer A, Kaplan LD, **Abrams DI**, Hadley WK, Yajko DM, Herndier BG. The usefulness of diagnostic bone marrow examination in patients with human immunodeficiency virus (HIV) infection. JAIDS 4:659-666, 1991.

55. Northfelt DW, Kaplan LD, **Abrams DI**. Continuous, low-dose therapy with interferon-alpha for human immunodeficiency virus (HIV)-related immune thrombocytopenic purpura. Am.J. Heme 38:238-239, 1991.

56. Slome LR, Moulton JM, Huffine C, Gorter R, **Abrams DI**. Physicians' attitudes toward assisted suicide in AIDS. JAIDS 5:712-718, 1992.

57. **Abrams DI**, Mitchell TF, Child CC, Shiboski SC, Brosgart CL, Mass M, and the Community Consortium. Clofazimine as prophylaxis for disseminated Mycobacterium avium complex. J Inf Dis 167:1459-63, 1993.

58. Jacobson MA, Owen M, Campbell J, Brosgart C, **Abrams DI**. Tolerance of combined ganciclovir and didanosine for cytomegalovirus disease associated with AIDS. Clin Infec Dis; 16 (suppl 1): S69-73, 1993.

59. Cotton DJ, Powderly WG, Feinberg J, **Abrams DI**, Chaisson RE, Joseph Wheat L, Finkelstein DM, Tallman V, Zimmer B, Berzon R, Fogelman I, and Phair J. Guidelines for the design and conduct of AIDS clinical trials. Clin. Infec Dis; 16:816-22, 1993.

60. Jacobson M, Besch C, Child C, Hafner R, Matts J, Muth K, Wentworth D, Neaton J, **Abrams DI**, et al. Prophylaxis with pyrimethamine for toxoplasmic encephalitis in patients with advanced HIV disease: Results of a randomized trial. J Inf Dis 169:384-94, 1994.

61. **Abrams DI**, Goldman A, Launer C, Korvick J, Neaton JD, Crane L, Grodesky M, Wakefield KM, Kornegay S, Cohn DL, Harris A, Luskin-Hawk R, Markowitz N, Sampson JH, Thompson M, Deyton L, and the Terry Beirn Community Programs for Clinical Research on AIDS, (CPCRA), NIAID, NIH, Washington, DC. Results of a randomized open-label comparison trial of ddI and ddC in HIV-infected patients who are intolerant of or have failed ZDV therapy: CPCRA 002. NEJM, 330:657-62, 1994.

62. Neaton JD, Wentworth D, Rhame F, Hogan C, **Abrams DI**, Deyton L, et al. Considerations in choice of a clinical endpoint for AIDS clinical trials. Statistics in Medicine, 13:2107-25, 1994.

63. Northfelt DW, Charlebois, ED, Mirda MI, Child C, Kaplan LD, **Abrams DI**, and the Community Consortium. Continuous low-dose interferon-alpha therapy for HIV-related immune thrombocytopenic purpura. JAIDS, 8:45-50, 1995.

64. Fleming TR, Neaton JD, Goldman A, DeMets DL, Launer C, Korvick J, **Abrams DI**. Lessons from the CPCRA ddI/ddC Trial. JAIDS, 10(Suppl.2):S9-S18, 1995.

65. Goldman AI, Carlin BP, Crane LR, Launer C, Korvick JA, Deyton L, **Abrams DI**. Response of CD4+ and clinical consequences to treatment using ddI or ddC in patients with advanced HIV infection. JAIDS, 11:161-169, 1996.

66. Brosgart CL, Mitchell T, Charlebois E, Coleman R, Mehalko S, and **Abrams DI**. Off-label drug use in HIV diseases. JAIDS, 12:56-62, 1996.

67. Burack JH, Cohen MR, Hahn JA and **Abrams DI.** A pilot randomized controlled trial of Chinese herbal treatment for HIV-associated symptoms. JAIDS, 12:386-93, 1996.

68. Saravolatz LD, Winslow D, Collins G, Hodges JS, Pettinelli C, Stein D, Markowitz N, Reves R, Loveless MO, Crane L, Thompson M, **Abrams DI**. A comparison of ZDV alone or in combination with didanosine or

zalcitabine in HIV-infected patients with AIDS or fewer than 200 CD4-positive cells per cubic millimeter. NEJM 335:1099-1106, 1996.

69. Slome LR, Mitchell TF, Charlebois E, Benevedes JM, **Abrams DI.** Physician-assisted suicide and patients with human immunodeficiency virus disease. NEJM, 336:417-421, 1997.
70. Deeks SG and **Abrams DI**. Genotypic resistance assays and anti-retroviral therapy. Lancet, 349:1489-90, 1997.
71. Brosgart C, Louis TA, Hillman D, Craig C, Alston B, Fisher E, **Abrams DI**, Luskin-Hawk R, Sampson J. A randomized, placebo-controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of cytomegalovirus disease in HIV- infected individuals. AIDS, 12:269-277, 1998.
72. Grant RM and **Abrams DI.** All is not dead in HIV-1 graveyard. Lancet, 351:308-09, 1998.
73. Leiser RJ, Mitchell TF, Hahn JA, Slome LR, **Abrams DI.** Nurses' attitudes and beliefs towards assisted suicide in AIDS. JANAC, 9:26-33, 1998.
74. **Abrams, DI**. Medical marijuana: Tribulations and trials. Journal of Psychoactive Drugs, 30:163-69, 1998.
75. Wheeler DA, Gibert CL, Launer CA, Muurahainen N, Elion RA, **Abrams DI**, Bartsch GE and the Terry Beirn Community Programs or Clinical Research on AIDS. Weight loss as a predictor of survival and disease Progression HIV infection. JAIDS, 18:80-85, 1998.
76. Cox L, Rouff JR, Markowitz M, Svedsen R, **Abrams DI.** Community Advisory Boards: Role in AIDS Clinical Trials. Health and Social Work, 23: 290-97, 1998.
77. El-Sadr W, Luskin-Hawk R, McCabe Yurik T, **Abrams D**, John SL, Sherer R, Crane L, Labriola A, Caras S, Pulling C, and Hafner R. A randomized trial of daily and thrice weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in HIV-infected individuals. CID 29:775-83, 1999.
78. Cohen MR, Mitchell TF, Bacchetti P, Child C, Crawford S, Gaeddert A and **Abrams DI**. Use of a Chinese herbal medicine for treatment of HIV-associated pathogen-negative diarrhea. Integrative Medicine, 2:79-84, 1999.
79. Brosgart CL, Mitchell TF, Coleman RL, Dyner T, Stephenson KE, **Abrams** DI. Clinical experience and choice of drug therapy for human immunodeficiency virus. Clin Infect Dis 28:14-22, 1999
80. Corless IB, **Abrams D**, Nicholas PK, McGibbon CA. The use of complementary and alternative therapies. AACN Clinical Issues 11:4-6,2000.
81. Baxter JD, Mayers DL, Wentworth DN, Neaton JD, Hoover ML, Winters M, Mannheimer S, Thompson M, **Abrams DI**, Brizz BJ, Ioannidis JPA, Merigan TC and the CPCRA 046 Study Team. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. AIDS, 14: F83-F93, 2000.
82. Eberly LE, Ohman PA, Neaton JD, Price RW, **Abrams DI**. Kaposi's sarcoma and CNS disease: a real association or an artifact of the control group? AIDS, 14:995-1000, 2000.
83. **Abrams DI**, Steinhart C, Frascino R. Epoetin alfa improves quality of life in HIV-infected patients. International Journal of STD & AIDS, 11:659-665, 2000.
84. Mulligan K, Tai VW, Algren H, **Abrams DI**, Leiser RJ, Lo JC, Scahmebelan M. Altered fat distribution in HIV-positive men on nucleoside analog reverse transcriptase inhibitor therapy. J Acquire Immune Defic Syndr Retrovirol, 26:443-448, 2001.
85. MacArthur RD, Chen L, Mayers D, Besch CL, Novak R, van den Berg-Wolf M, Yurik T, Peng G, Schmetter B, Brizz B, **Abrams D**. The rationale and design of the CPCRA (Terry Beirn Community Programs for Clinical Research on AIDS) 058 FIRST (Flexible Initial Retrovirus Suppressive Therapies) Trial. Controlled Clinical Trials, 22:176-90, 2001.
86. Kosel BW, Aweeka FT , Benowitz NL, Shade SB, Hilton JF, Lizak PS, **Abrams DI**. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. AIDS, 16:543-550, 2002.
87. **Abrams DI**, JD Bebchuk, ET Denning, RT Davey, L Fox, HC Lane, J Neaton, J Sampson, R Verheggen, D Zeh, and N Markowitz for the Terry Beirn Community Programs for Clinical Research on AIDS. A

randomized open-label study of the impact of two different doses of subcutaneous recombinant IL-2 on viral burden in patients with HIV-1 infection and CD4+ counts > 300/mm3: CPCRA 059. JAIDS, 29:221-231, 2002.

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"B"

Medicinal cannabis: Rational guidelines for dosing

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The medicinal value of cannabis (marijuana) is well documented in the medical literature. Cannabinoids, the active ingredients in cannabis, have many distinct pharmacological properties. These include analgesic, anti-emetic, anti-oxidative, neuroprotective and anti-inflammatory activity, as well as modulation of glial cells and tumor growth regulation. Concurrent with all these advances in the understanding of the physiological and pharmacological mechanisms of cannabis, there is a strong need for developing rational guidelines for dosing. This paper will review the known chemistry and pharmacology of cannabis and, on that basis, discuss rational guidelines for dosing.

Keywords Cannabinoids, cannabis, dosing, marijuana, pharmacology

Introduction and brief historical background

Possibly the first references to the medicinal use of cannabis are found in the Chinese pharmacopoeia of Emperor Shen-Nung, written in 2737 BC. This document recommended cannabis for analgesia, rheumatism, beriberi, malaria, gout and poor memory [1]. Eastern Indian documents in the Atharvaveda, dating to about 2000 BC, also refer to the medicinal use of cannabis [2]. Archeological evidence has been found in Israel indicating that cannabis was used therapeutically during childbirth as an analgesic [3]. This use of cannabis continued in the West until the mid-1880s and continues today in parts of Asia. In ancient Greece and Rome, both the Herbal of Dioscorides and the writings of Galen refer to the use of medicinal cannabis [4].

The medicinal use of cannabis in western medicine occurred much later. There is mention of it in a treatise by Culpepper written in medieval times. British East India Company surgeon William O'Shaughnessy introduced cannabis for medicinal purposes into the United Kingdom following observations he made while working in India in the 1840s. He used it in a tincture for a wide range of uses, including analgesia [5], and Queen Victoria used cannabis for relief of dysmenorrhoea in the same era [6•]. In 1937, against the advice of the majority of the medical community and much of the American Medical Society, the federal government criminalized non-medical cannabis. Cannabis was removed from the United States Pharmacopoeia in 1942 which, up until that time, had still been prescribed by physicians [7].

The physiological mechanisms and therapeutic value of cannabinoids continue to be well documented in the medical literature [6•,7-11,12••,13,14,15••,16••,17••,18••,19-21,22••, 23, 24••,25-27,28•,29,30,31••,32-36]. However, there has been little written on appropriate dosing regimens for the medicinal use of cannabis. With current and emerging laws allowing physicians in many areas of the world to recommend the use of cannabis to treat symptoms of certain diseases and medical conditions, there is a need for medical literature describing rational dosing guidelines. This paper will review the known chemistry and pharmacology of cannabis and then, on that basis, discuss rational guidelines for dosing.

Chemistry and pharmacology of cannabis

Cannabis is a complex plant, with several existing phenotypes, each containing over 400 chemicals [14,15••]; approximately 60 are chemically unique and classified as plant cannabinoids [11,15••]. Naturally occurring cannabinoids are also produced in the human body [8]. The cannabinoids are 21-carbon terpenes, biosynthesized predominantly via a recently discovered deoxyxylulose phosphate pathway [16••], and are lipophilic. Δ^9-tetrahydrocannabinol (THC) and Δ^8-THC appear to produce the majority of the psychoactive effects of cannabis. Δ^9-THC, the active ingredient in dronabinol (Marinol) is the most abundant cannabinoid in the plant and this has led researchers to hypothesize that it is the main source of the effects of the drug [15••]. Dronabinol is available by prescription as a schedule III drug.

Other major plant cannabinoids include cannabidiol and cannabinol, both of which may modify the pharmacology of THC and have distinct effects of their own. Cannabidiol is the second most prevalent active ingredient in cannabis and may produce most of its effects at moderate, mid-range doses. Cannabidiol converts to THC as the plant matures and over time this THC over time degrades to cannabinol [15••]. Up to 40% of the cannabis resin in some strains is cannabidiol [15••]. The amount varies according to plant; some varieties of *Cannabis sativa* have been found to contain no cannabidiol [6•]. As cannabidiol may help reduce anxiety symptoms, cannabis strains without cannabidiol may produce more panic or anxiogenic side effects. Cannabidiol may exaggerate some of the effects of THC (including

increasing THC-induced euphoria), while attenuating others, and competitively slows THC metabolism in the liver. Consequently, a dose of THC combined with cannabidiol will create more psychoactive metabolites than the same dose of THC alone [14,15••]. In mice, pre-treatment with cannabidiol increased brain levels of THC by ~ 3-fold and there is strong evidence that cannabinoids can increase the brain concentration and pharmacological actions of other drugs [16••,17••]. Some researchers have proposed that many of the negative side effects of dronabinol, including sedation and altered mental activity, could be reduced by combining it with cannabidiol or possibly other non-psychoactive cannabinoids [8].

Much less is known about cannabinol, although it appears to have pharmacological properties that are quite different from cannabidiol. Cannabinol has significant anticonvulsant, sedative and other pharmacological activities that are likely to interact with the effects of THC [14]. Cannabinol may induce sleep and may provide some protection against seizures for epileptics [15••,16••,17••].

Two physiologically occurring lipids, anandamide (AEA) and 2-arachidonylglycerol (2-AG), have been identified as endogenous cannabinoids (endocannabinoids), although there are likely to be more [18••]. The physiological roles of these endocannabinoids have been only partially clarified but available evidence suggests that they function as diffusible and short-lived intercellular messengers that modulate synaptic transmission. Recent studies have provided strong experimental evidence that endocannabinoids mediate signals retrogradely from depolarized post-synaptic neurons to presynaptic terminals to suppress subsequent neurotransmitter release, driving the synapse into an altered state [18••,19,20]. Signaling by the endocannabinoid system appears to represent a mechanism by which neurons can communicate backwards across synapses to modulate their inputs.

There are two known cannabinoid receptor subtypes. Subtype 1 (CB_1) is expressed primarily in the brain whereas subtype 2 (CB_2) is expressed primarily in the immune system [10,20]. Cannabinoid receptors constitute a major family of G protein-coupled, seven-helix transmembrane nucleotides, are similar to the receptors of other neurotransmitters such as dopamine, serotonin and norepinephrine, and are the most abundant G protein-coupled receptor in the brain [8,10,11]. Activation of protein kinases may be responsible for some of the cellular responses elicited by the CB_1 receptor [21].

Because of this biochemical complexity, characterizing the clinical pharmacology of cannabis is challenging. Further complicating the evaluation of cannabis is the variable potency of the plant material used in research studies. The concentration of THC and other cannabinoids in cannabis varies greatly depending on growing conditions, plant genetics and processing after harvest [19]. The highest concentrations of bioactive compounds are found in the resin exuded by the flowering female plants [18••,19]. Leaf mixtures of cannabis have concentrations of THC ranging from 0.3 to 4% by weight [18••,19,20]. However, cannabis today is typically distributed as flowers and can contain 8 to ≥ 25% of THC. Thus, 1 g of cannabis flowers would typically contain 80 to 250 mg of THC [19].

The clinical pharmacology of cannabis containing high concentrations of THC may differ from plant material containing small amounts of THC and higher amounts of the other cannabinoids. Moreover, the bioavailability and pharmacokinetics of inhaled cannabis are substantially different than when cannabis is ingested [17••,18••].

Clinical pharmacology

Although it is a potent drug that may produce psychoactive effects, THC (and the other cannabinoids) has relatively low toxicity, and lethal doses in humans have not been described [23,24••]. The theoretical LD_{50} value is estimated to be 1 to 20,000 or 1 to 40,000, using a single cannabis cigarette as a unit of dose. Conversely stated, a human would have to consume 20,000- to 40,000-fold the amount of cannabis contained in one cigarette, in a short period of time, to achieve lethality. Using this as a basis, it has been estimated that ~ 628 kg of cannabis would have to be smoked in 15 min to induce a lethal effect [25].

Central effects of cannabinoids include disruption of psychomotor behavior, short-term memory impairment, intoxication, stimulation of appetite, antinociceptive actions (particularly against pain of neuropathic origin) and anti-emetic effects. Although there are signs of mild cognitive impairment in chronic cannabis users there is little evidence that such impairments are irreversible, or that they are accompanied by drug-induced neuropathology. A proportion of regular users of cannabis will develop some tolerance [37]. A study by Hart and co-workers demonstrated that acute cannabis smoking produced minimal effects on complex cognitive task performance in experienced cannabis users, while still subjectively providing a euphoric 'high' [38••]. The potential medical applications of both natural and synthetic cannabinoids are currently being tested in a number of clinical trials.

Delivery system and pharmacokinetics

The route of administration is an important determinant of the pharmacokinetics of the cannabinoids in cannabis, particularly absorption and metabolism [39-42]. Typically, cannabis is smoked as a cigarette with a mass of between 0.5 and 1.0 g. After combustion and inhalation, peak venous blood levels of 75 to 150 ng of THC per ml of plasma have been measured when smoking is finished [39,43,44]. The main advantage of smoking is rapid onset of effect and ease of dose titration. When cannabis is smoked, cannabinoids in the form of an aerosol in the inhaled smoke are absorbed and delivered to the brain rapidly, as would be expected of a highly lipid-soluble drug [41,45].

Individual smoking behavior during an experiment is difficult for a researcher to control, and smoking behavior is not easily standardized, although some research protocols for standardization of smoking have been developed [44]. An experienced cannabis smoker can titrate and regulate dose to obtain the desired acute effects and to minimize

undesired effects [46,47]. Each inhalation delivers a discrete dose of cannabinoids to the body. Inhalation volume changes with phase of smoking, tending to be highest at the beginning and lowest at the end of smoking a cigarette. Some studies found frequent users to have higher inhalation volumes than less frequent cannabis users. Heavy users could absorb as much as 27% of available THC, which may be twice as much as an infrequent user may absorb [47]. During smoking, as the cigarette length shortens, the concentration of THC in the remaining cannabis increases. Thus, each successive inhalation contains an increasing concentration of THC [47]. However, up to 40% of the available THC may be completely combusted in the process of smoking and may not be biologically available. Assays of cannabinoids in blood or urine after smoking can partially quantify dose actually absorbed, but the analytic procedures are methodologically demanding [47,48].

After smoking, venous blood levels of THC fall precipitously within minutes, and an hour later they are ~ 5 to 10% of the peak level [40,41,43,44]. Plasma clearance of THC is ≥ 950 ml/min which is quite high and is essentially the rate of hepatic blood flow. However, the rapid disappearance of THC from blood is largely due to redistribution to other tissues in the body rather than cannabinoid metabolism [40,41]. Metabolism in most tissues is relatively slow. Slow release of cannabinoids from tissues and subsequent metabolism results in a long elimination half-life. The terminal half-life of THC is estimated to range from ~ 20 h to as long as 10 to 13 days, although reported estimates vary considerably and are likely to reflect the sensitivity of the measurement assay.

Smoking anything, including cannabis, is not beneficial for the health of the lungs and airway system [49,50]. A healthier option may be vaporization; because cannabinoids are volatile, they will vaporize at a temperature much lower than actual combustion [51]. Heated air can be drawn through cannabis, the active compounds will vaporize, and these can then be inhaled. Vaporization delivers the substance in a rapid manner that, like smoking, can be easily titrated to the desired effect [9]. Theoretically this removes most of the health hazards of smoking, although this has not yet been studied. Furthermore, there may be differing vaporization points for the individual cannabinoids. Vaporized cannabis may have differing concentrations and ratios of cannabinoids compared to smoked cannabis, although this also needs further study.

Cannabis can also be ingested orally or through a feeding tube. Orally ingested THC or cannabis has quite different pharmacokinetics than when it is inhaled. The onset of action is delayed and titration of dosing is more difficult [52-54,55•]. Maximum THC and other cannabinoid blood levels are only reached 1 to 6 h after an oral dose, with a half-life of 20 to 30 h [52-54,55•]. This is also reflected in the pharmacokinetics of dronabinol capsules, which contain only synthetic THC and none of the other cannabinoids [54]. When orally ingested, THC is degraded in the liver to the byproduct 11-hydroxy-THC, which also has potent psychoactive effects. This metabolite occurs at a much lower concentration when cannabis is inhaled. Thus, when THC (dronabinol or cannabis) is ingested orally, more sedation occurs because of the presence of 11-hydroxy-THC psychoactive metabolite [54].

Metabolism, bioavailability and drug interactions

Some inactive carboxy metabolites have terminal half-lives of 50 h to ≥ 6 days and thus serve as markers of prior cannabis use in urine tests [55•,56]. Most of the absorbed THC dose is eliminated in feces, and ~ 33% is eliminated in urine. THC enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-Δ^9-THC (9-COOH-9-THC). The glucuronide is excreted as the major urine metabolite along with ~ 18 non-conjugated metabolites. Frequent and infrequent cannabis users are similar in the way that they metabolize THC [53].

THC bioavailability from smoked cannabis varies greatly among individuals and also depends on the composition of the specific cannabis preparation. Bioavailability can range from 1 to 27%, with variable bioavailability resulting from significant loss of THC in side stream smoke, as well as variation in individual smoking behaviors. This includes incomplete absorption from inhaled smoke, metabolism in lung, and cannabinoid pyrolysis (ie, destruction by combustion).

Cannabinoids appear to partially inhibit the metabolism of drugs metabolized by the hepatic cytochrome P450 enzyme system [57,58,59••,60]. Thus, the absorption or clearance of other drugs taken with cannabis may be slowed or hastened depending on timing and sequence of drug ingestion and past exposure. THC is highly bound to plasma proteins (97 to 99%) and is likely to interact with other highly bound drugs because of competition for binding sites on plasma proteins [61,62].

The Food and Drug Administration (FDA) first licensed and approved dronabinol in 1986 for the treatment of nausea and vomiting associated with chemotherapy. The indication was expanded in 1992 to the treatment of anorexia associated with weight loss in patients with AIDS wasting syndrome. In a randomized, double-blind, placebo-controlled, 6-week study involving 139 patients, dronabinol provided a statistically significant improvement in appetite and non-statistically significant trends toward improved body weight and mood, and decreases in nausea [63•]. In 1999, the United States Drug Enforcement Administration, in cooperation with the FDA, reclassified the scheduling status of dronabinol from a Schedule II (CII) to a Schedule III (CIII) controlled substance (for definitions of schedules, refer to *http://www.dea.gov/pubs/csa/812.htm*).

In 454 patients with cancer who received a total of 750 courses of treatment for various malignancies, dronabinol capsules provided complete or partial success in easing nausea and vomiting in 68% of patients given < 7 mg/m^2/day of dronabinol and 64% of patients given > 7 mg/m^2/day of dronabinol [64].

According to the manufacturer, Unimed Pharmaceuticals Inc, the prescribed dose of dronabinol for appetite

stimulation is 2.5 mg twice-daily, to be taken before lunch and dinner. For nausea, vomiting and pain the dosing is 5 mg/m^2. If the 5 mg dose is ineffective, incremental increases of 2.5 mg, up to a maximum of 15 mg, is recommended. The same dose can be taken every 2 to 4 h for a maximum of four to six doses a day. Regardless of the clinical setting in which it is prescribed, the maximum total recommended dose of dronabinol is 15mg/m^2 four- to six-times daily or ~ 100 to 120 mg a day [65].

Clinical trials

There are a limited number of well-performed clinical trials from which to draw succinct dosing regimens. Clinical trials have typically used cannabis cigarettes supplied by the NIDA (National Institute on Drug Abuse) containing 3.5 to 4.0% of THC by weight [59••,66,67]. Recently, Abrams and co-workers conducted an open-label study in patients with confirmed HIV neuropathy with persistent neuropathic pain [68]. All patients had prior experience of smoking marijuana but had ceased for 30 days prior to admission. After a 2-day lead-in period, patients smoked one cigarette containing 3.56% of THC three-times daily for 7 days. A heat-capsaicin-induced experimental pain model was used to clarify the effects of THC. Marijuana smoking led to a reduction in pain score to 20/100, with ten of 16 patients experiencing a 30% reduction in average daily pain. An excellent correlation was noted in the response to the heat-capsaicin model, as 14 of 16 patients experienced a 30% reduction in the area of secondary hyperalgesia after smoking [68].

Wade and co-workers compared plant-derived cannabis extracts to standard treatments for neurogenic symptoms unresponsive to standard treatment in a double-blind, randomized, placebo-controlled, cross-over trial with 2-week treatment periods [69]. The enrolled patients (n = 24) had multiple sclerosis (n = 18), spinal cord injury (n = 4), brachial plexus injury (n = 1) and limb amputation due to neurofibromatosis (n = 1). Whole-plant extracts of either THC only, cannabidiol only, a mixed cannabinoid extract of both THC and cannabidiol in a 1:1 ratio, or a matched placebo were self-administered by sublingual spray at doses determined by titration against symptom relief or unwanted effects within the range of 2.5 to 120 mg/24 h. The results demonstrated that pain relief associated with both THC and cannabidiol was significantly superior to placebo. The mixed cannabinoid extract, compared to placebo, was significantly superior in providing pain relief and improving bladder control, muscle spasms and spasticity. Side effects were rare. Three patients had transient hypotension and intoxication with rapid initial dosing of the THC extract.

Deriving dosing recommendations and guidelines

Cannabis has many variables that do not fit well with the typical medical model for drug prescribing. If the plant is used, the variations are extreme. Plants vary immensely by phenotypes, and even the time of harvest affects which cannabinoids are present and in what percentages. An individual may be much more sensitive than another, heavy smokers may experience different chemical effects than light smokers and ingestion may alter bioavailability. The bulk of the research into cannabis has primarily examined THC, the other cannabinoids have been studied to a lesser degree, while little research has been performed on combinations of cannabinoids, although this is beginning to change. These combinations are important to medicinal users of cannabis as a number of positive synergistic effects could be involved [70-72]. All of these points make it imperative that the dosing is highly individualized, so a patient-determined, self-titrated dosing model is recommended. This self-titration model is acceptable given the variables discussed above, as well as the low toxicity of cannabis. This construct is not unique to cannabis. There are other drugs that have relatively low toxicity and high dosing limits (gabapentin being one notable example), and are titrated to effect.

To facilitate an understanding of the determination of these guidelines, an estimate of the actual amount of THC obtained by a patient when smoking different strengths of cannabis must be derived. As noted earlier, with smoking as the delivery, 40% of the active ingredients are lost in side stream or combustion, and a maximum of 27% of the remaining active ingredients can actually be absorbed by the patient. Given this, the maximum THC absorbed by a patient using 1 g of cannabis containing 10% of THC would be 16.3 mg.

The only form of cannabinoid that is available by a formal, dose-specific prescription is dronabinol. There are too many variables in the published clinical trials and case series with raw cannabis to use those studies as a basis for deriving doses. Therefore, we will use the dronabinol prescription guidelines as published by the manufacturer and accepted by the FDA as the basis for formulating our dosing recommendations for natural cannabis. It is critical to note that dronabinol is an oral preparation and contains only THC. Most medicinal cannabis patients use smoking as the route of delivery. As we have previously noted there are significant differences in pharmacokinetics between oral consumption and smoking. Furthermore, there are varying physiological effects when the other cannabinoid forms are present, as is the case with natural cannabis plant material. It is also not clear how the original dosing construct for dronabinol was arrived at, although we assume it was derived from clinical testing for therapeutic benefit versus side effects. Despite these inherent limitations, these calculations do provide approximate dose equivalents by weight and are useful as long as one recognizes these limitations.

Applying the known pharmacokinetics of cannabis, as described above, to a conservative dronabinol dosing model of 2.5 to 60 mg/day, we calculated the following doses for cannabis containing these particular percentages of THC (Table 1).

These derived figures lie closely within the range of reported amounts. In informal surveys from patients in Washington and California (USA), the average reported consumption of cannabis by medicinal users typically ranges between 10 to 20 g of raw cannabis per week, or ~ 1.42 to 2.86 g/day of cannabis. The average strength of medical cannabis used by the patients who reported these doses was 15% THC. Thus, these patients were actually absorbing between 34 and 68 mg/day of THC from the raw

cannabis. The mean strength of medical cannabis in this study was ~ 19% THC, which corresponds to 44 to 88 mg/day of THC actually being consumed by the patient [72]. These figures are all within a similar range.

Table 1. Amount of cannabis calculated to contain equivalent amounts of THC to dronabinol (2.5 to 60 mg).

% of THC in cannabis	Amount of cannabis (g) required to obtain:			
	2.5 mg of THC	10 mg of THC	30 mg of THC	60 mg of THC
5%	0.60	1.24	3.70	7.40
10%	0.30	0.62	1.85	3.70
15%	0.16	0.41	1.23	2.46
20%	0.10	0.31	0.93	1.86
25%	0.08	0.25	0.75	1.50
30%	0.05	0.20	0.62	1.24

Our recommended doses are further reinforced by two studies that utilized smoked cannabis in a well-documented dosing regime. Chang and co-workers studied the effects of smoked cannabis dosed at 10 mg/m^2 five-times-daily, which is equivalent to 87.5 mg of THC per day for an average-sized person. This would be the equivalent of 3.6 g of cannabis containing 15% of THC [73]. Vinciguerra and co-workers studied smoked cannabis dosed at 5 mg/m^2 four-times-daily, or 35 mg of THC a day for an average person. This is the equivalent of ~ 1.4g of cannabis containing 15% of THC [74]. For the purposes of these calculations, we assumed an average-sized person to be 1.70 m in height with a mass of 63.6 kg and a body surface area of 1.75 m^2.

These doses all fall within the medical cannabis guidelines allowed in the Canadian medical system. The Canadian medical allowance for cannabis is for 1 to 12 g/day, with an average of > 5 g. These doses are also highly similar to the dosing range reported in a recent survey of patients who use cannabis to control symptoms of amyotrophic lateral sclerosis [75]. Thus, despite all of the noted variables, there is remarkable consistency among our derived doses and the reported doses from a number of different sources noted here.

A final comment should be made regarding physiological tolerance to cannabinoids. Tolerance plays a significant role in cannabis use since tolerance may develop to any of the various cannabinoids [76]. With regard to treating chronic, intractable pain, physicians will often prescribe increasingly larger doses of long-acting opioids as patients develop tolerance. These patients are also generally prescribed fast onset, short-acting opioids for 'breakthrough pain'. This is accepted practice, despite the fact that opioids, even in an opioid-dependent patient, have the capacity to suppress breathing to the extent of inducing respiratory arrest. Long-term cannabis users can develop tolerance but, as previously discussed, there is essentially no risk for overdose. Thus, it is conceivable that a long-term cannabis user may require significantly larger amounts of cannabis to achieve a therapeutic effect. In addition, those who ingest cannabis may also require significantly higher amounts. Until more refined and purified cannabinoid preparations are available it will not be possible to derive a more specific or exact dosing schedule.

Conclusions

We have outlined reasonable guidelines for dosing of medical cannabis, based on the known pharmacology. Our dosing model is primarily derived from dronabinol (THC), since that is the only clearly defined, FDA approved dosing paradigm currently available. However, our derived dosing schedule did match reasonably well with the amounts of natural cannabis reported by medical users. In using our dosing guidelines clinicians must be aware that THC is not the only clinically useful and pharmacologically active cannabinoid. The effects of THC are clearly modulated by other cannabinoids, which may have unique effects of their own. The clinician must also be aware of patient tolerance, and differing routes of intake and delivery systems, which can affect pharmacokinetics and bioavailability. Recognizing this, we recommend that our guidelines are used as a construct to allow the physician and patient to develop an individual, self-titration dosing paradigm. Given the current state of the known, published pharmacology of cannabis, this is the best dosing model that can be derived.

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Short-Term Effects of Cannabinoids in Patients with HIV-1 Infection

A Randomized, Placebo-Controlled Clinical Trial

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Background: **Cannabinoid use could potentially alter HIV RNA levels by two mechanisms: immune modulation or cannabinoid–protease inhibitor interactions (because both share cytochrome P-450 metabolic pathways).**

Objective: **To determine the short-term effects of smoked marijuana on the viral load in HIV-infected patients.**

Design: **Randomized, placebo-controlled, 21-day intervention trial.**

Setting: **The inpatient General Clinical Research Center at the San Francisco General Hospital, San Francisco, California.**

Participants: **67 patients with HIV-1 infection.**

Intervention: **Participants were randomly assigned to a 3.95%-tetrahydrocannabinol marijuana cigarette, a 2.5-mg dronabinol (delta-9-tetrahydrocannabinol) capsule, or a placebo capsule three times daily before meals.**

Measurements: **HIV RNA levels, $CD4^+$ and $CD8^+$ cell subsets, and pharmacokinetic analyses of the protease inhibitors.**

Results: **62 study participants were eligible for the primary end point (marijuana group, 20 patients; dronabinol group, 22 patients; and placebo group, 20 patients). Baseline HIV RNA level was less than 50 copies/mL for 36 participants (58%), and the median $CD4^+$ cell count was 340×10^9 cells/L. When adjusted for baseline variables, the estimated average effect versus placebo on change in $\log_{10}$ viral load from baseline to day 21 was −0.07 (95% CI, −0.30 to 0.13) for marijuana and −0.04 (CI, −0.20 to 0.14) for dronabinol. The adjusted average changes in viral load in marijuana and dronabinol relative to placebo were −15% (CI, −50% to 34%) and −8% (CI, −37% to 37%), respectively. Neither $CD4^+$ nor $CD8^+$ cell counts appeared to be adversely affected by the cannabinoids.**

Conclusions: **Smoked and oral cannabinoids did not seem to be unsafe in people with HIV infection with respect to HIV RNA levels, $CD4^+$ and $CD8^+$ cell counts, or protease inhibitor levels over a 21-day treatment.**

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Marijuana has been smoked for medicinal purposes for centuries (1). Introduced into western medicine in 1842, marijuana was used to treat various illnesses on the basis of its purported analgesic, anticonvulsant, sedative, hypnotic, and antispasmodic properties. With the passage of the Marihuana Tax Act in 1937, use of marijuana as a therapeutic agent in the United States waned until the substance was removed from the U.S. Pharmacopoeia in 1942. The Controlled Substances Act of 1970 placed marijuana in the Schedule I category along with other substances deemed to have no medicinal value and high potential for abuse.

In 1986, the U.S. Food and Drug Administration approved a synthetic, oral form of marijuana's main psychoactive component, delta-9-tetrahydrocannabinol (dronabinol, Marinol, Roxane Laboratories, Columbus, Ohio), for treating chemotherapy-induced nausea and vomiting (2–5). A randomized, controlled trial demonstrated that dronabinol increased self-reported appetite but not weight in patients with AIDS-related wasting syndrome; these findings led to an expansion of the labeling indication for this use in 1992 (6, 7). Before the advent of highly active antiretroviral therapy in the 1990s, many patients infected with HIV-1 experienced wasting as a preterminal manifestation of the disease (8). Patients with AIDS-related wasting syndrome often reported that they preferred smoked marijuana to dronabinol because it was easier to titrate the dose to achieve the desired effect; smoked marijuana delivers cannabinoids to the bloodstream much more rapidly than dronabinol (9). By the mid-1990s, cannabis buyers' clubs in the San Francisco Bay area were reportedly selling marijuana to 11 000 patients with HIV infection (10–12).

With the increased availability of protease inhibitor–containing antiretroviral regimens in the mid-1990s, the incidence of AIDS-related wasting syndrome decreased markedly, as did most of the other late-stage opportunistic manifestations of advanced HIV disease (13–15). Protease inhibitors, which can inhibit or stimulate the hepatic cytochrome P-450 enzyme system, are subject to many significant drug–drug interactions with other agents used in treating HIV infection and its complications (16, 17). The potential for a drug–drug interaction between protease inhibitors and marijuana is worrisome since many HIV-infected patients continue to smoke marijuana as an appetite stimulant or to decrease nausea associated with their antiretroviral therapy (18, 19). The likelihood of such an interaction is supported by the facts that cannabinoids are metabolized by some of the same cytochrome P-450 enzyme isoforms that metabolize the more widely prescribed protease inhibitors and that tetrahydrocannabinol has been shown to inhibit the metabolism of other drugs (20–23).

Although few recent clinical trials have evaluated the potential therapeutic effects of smoked marijuana, significant progress has been made in understanding the pharmacology of cannabinoids in humans. Of the two cannabinoid receptors identified, CB1 (found mainly in cells of the central nervous system) is thought to be responsible for the neurologic and behavioral effects of marijuana (24, 25).

The identification of a CB2 receptor, found predominantly on B lymphocytes and natural killer cells, suggests that cannabinoids may also affect the immune response. Some studies suggest that marijuana can impair the immune system through B-lymphocyte modulation, tumor necrosis factor inhibition, or changes in the phenotype and function of circulating lymphocytes (26–29).

The hallmark of successful antiretroviral therapy is sustained suppression of HIV RNA levels associated with increasing $CD4^+$ cell counts (30–32). Considering the potential for both a protease inhibitor–cannabinoid interaction and an effect of smoked marijuana on the immune system, we designed a study to determine the safety or toxicity profile of cannabinoids (smoked and oral) in persons with HIV infection. We chose HIV RNA levels as our primary outcome because an intervention that interacted unfavorably with either the antiretroviral agent pharmacokinetics or the immune system directly could cause a perturbation of viral suppression. We report the overall safety results of this randomized, controlled inpatient clinical trial.

Context

Because the same systems metabolize cannabinoids and protease inhibitors, cannabinoids might alter viral loads in HIV-infected patients taking protease inhibitors.

Contribution

In this randomized trial, 62 HIV-infected patients taking indinavir or nelfinavir received a marijuana cigarette, dronabinol capsule, or placebo capsule three times daily for 21 days. Half of the patients in all three groups had undetectable viral loads during the study, and average changes in viral load with marijuana and dronabinol, relative to placebo, were small.

Cautions

The findings of no large harmful effects on viral loads with either smoked or oral cannabinoids need to be confirmed in larger and longer trials.

–The Editors

METHODS

Study Group

Study participants were recruited by referrals from local physicians and advertisements in newspapers. Volunteers from across the country telephoned to determine whether they might be eligible to participate. Participants were required to be at least 18 years of age, have documented HIV infection, and be receiving a stable antiretroviral treatment regimen of either indinavir (Crixivan, Merck & Co., Inc., North Wales, Pennsylvania) or nelfinavir (Viracept, Agouron Pharmaceuticals, Inc., La Jolla, California) for at least 8 weeks before enrollment. When enrolled, participants who had been taking the recently recommended dose of nelfinavir, 1250 mg twice daily, were switched to 750 mg three times daily for consistency of our pharmacokinetic evaluations (33). No additional protease inhibitors were allowed for the duration of the study. Participants were also required to have a stable viral load, defined as less than a threefold (0.5 $\log_{10}$) change in HIV RNA level for the 16 weeks before enrollment. All participants were required to have previous experience smoking marijuana (defined as six or more times) to ensure that they knew how to inhale and what neuropsychiatric effects to expect. The institutional review board of the University of California, San Francisco, approved the study, and signed, informed consent was obtained from each participant before enrollment.

Exclusion criteria included any active opportunistic infection or malignant condition requiring acute treatment, unintentional loss of 10% or more of body weight during the previous 6 months, current substance dependence ascertained by completion of a confidential drug screening form and an alcohol screening form, methadone maintenance, use of tobacco or cannabinoids (smoked or oral) within 30 days of enrollment, history of serious pulmonary disease, pregnancy, or stage II or higher AIDS dementia complex. Laboratory exclusion criteria were hematocrit less than 0.25 and elevation of hepatic aminotransferase levels to greater than five times the upper limit of normal. Therapeutic exclusions were concurrent use within the past 8 weeks of anabolic hormones, prednisone, interleukin-2, or other agents known to alter immune system function.

Study Medications

The National Institute on Drug Abuse provided prerolled marijuana cigarettes, weighing on average 0.9 g and containing 3.95% delta-9-tetrahydrocannabinol. These cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the General Clinical Research Center at the San Francisco General Hospital, where the inpatient study was conducted. The frozen marijuana cigarettes required rehydration overnight in a humidifier. Participants randomly assigned to the smoked marijuana group were housed in a room with a fan ventilating to the outside. To maximize standardization of inhaled doses, research staff monitored participants while they followed the uniform puff procedure outlined by Foltin and colleagues (34). Research staff weighed the marijuana cigarettes immediately before and after they were administered to participants and returned all leftover material to the pharmacy. Study participants smoked up to three complete marijuana cigarettes daily, as tolerated, 1 hour before meals. Study participants were randomly assigned in a double-blind fashion to the oral regimens, which were given on the same schedule as the smoked marijuana. Research staff observed participants taking all treatments.

Research Design and Procedures

Study clinicians admitted study participants to the General Clinical Research Center for a 4-day lead-in period to obtain baseline variables. A urine sample obtained on the day of admission (day −4) had to be negative for tetrahydrocannabinol. The second phase of the trial was a 21-day intervention period beginning with random assignment of treatments on day 0. Patients were stratified by protease inhibitor (indinavir or nelfinavir) and then allocated with equal probability in blocks of 12 to the study agents (marijuana, dronabinol, and placebo). The statistician generated the random allocation sequences, and the pharmacists maintained the sequences in a secure location and distributed the assignments to the study coordinator on day 0.

Study participants were not permitted to have visitors or to leave the General Clinical Research Center unless accompanied by research personnel during the 25-day study. All clinical laboratory tests and study procedures were obtained or performed in the center. Patients were weighed on the same calibrated scale each morning while wearing a hospital gown.

Baseline blood specimens were collected on days −4 and 0 to examine within-participant variation in HIV RNA level in the absence of experimental therapies. Follow-up specimens were obtained on days 2, 5, 8, 11, 14, 17, 19, and 21. Samples were stored at −70 °C and batch-tested for HIV RNA at the end of the trial by using branched DNA (bDNA) technology (VERSANT HIV-1 RNA 3.0 Assay, Bayer Diagnostics, Emeryville, California) with a lower detection limit of 50 copies/mL.

Baseline samples for $CD4^+$ and $CD8^+$ cell counts were collected on days −4 and 0, and follow-up specimens were drawn on days 7, 14, and 21. Assays were performed in the San Francisco General Hospital Clinical Laboratory. Complete blood counts with differential were performed by using an automated hematology analyzer (Bayer Technicon H3 system, Bayer Corp., Tarrytown, New York) according to the manufacturer's directions. The $CD4^+$ and $CD8^+$ cell counts were measured by using MultiTEST CD3/CD8/CD45/CD4 with Trucount tubes (BD Biosciences, San Jose, California) according to the manufacturer's directions. Data acquisition and analysis were performed by using a FACSCalibur (BD Biosciences) flow cytometer and MultiSET software (BD Biosciences).

Pharmacokinetic methods are described elsewhere (35).

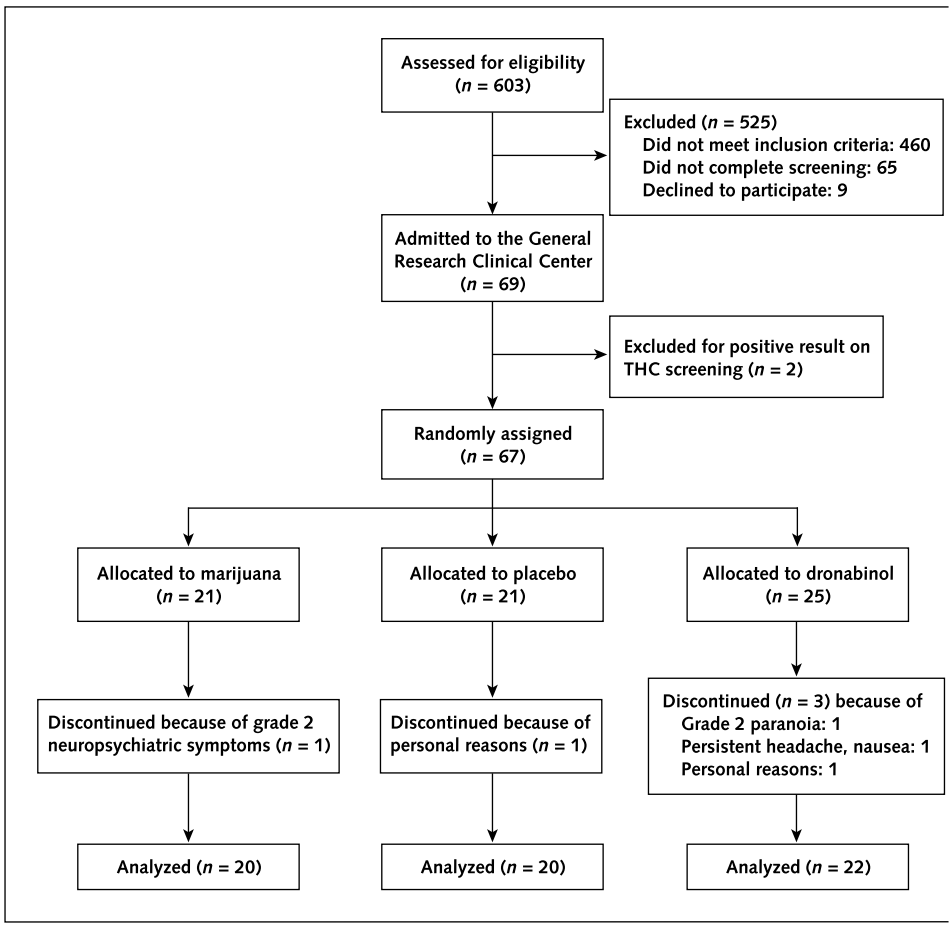
Statistical Analysis

This randomized trial was designed to compare the marijuana and dronabinol groups with the placebo group with respect to mean changes in $\log_{10}$ HIV RNA levels between days 0 and 21. We planned the sample size for two one-sided Bonferroni-adjusted 0.05-level *t*-tests of the null hypothesis of no difference against the alternative that the cannabinoid effect is larger than 0.3 $\log_{10}$ copies/mL, each with 80% power. This design, which assumed an SD of 0.3 $\log_{10}$ copies/mL for within-participant changes, required 21 participants per group. To allow for potential dropouts, we enrolled two additional patients per group. The between-group difference of 0.3 $\log_{10}$ copies/mL represents a doubling of the viral load on the natural scale and a clinically significant and potentially unsafe effect of cannabinoid on HIV RNA levels (30). Changes less than 0.3 $\log_{10}$ copies/mL are considered to be within the natural range of variability of $\log_{10}$ HIV RNA measurements (36, 37).

To evaluate the success of the randomization procedures, we examined the distributions by group of several baseline variables, including $CD4^+$ and $CD8^+$ cell counts and HIV RNA levels on day 0 and protease inhibitor used. When a participant's viral load level was undetectable, a value of 49 copies/mL was assumed. HIV RNA levels were transformed to the $\log_{10}$ scale, and each participant's change in viral load level on day 21 relative to day 0 was calculated. We summarized the raw changes by group by using means, 95% CIs of differences between mean changes, and *P* values. We used multiple regression to model the cannabinoid effects while controlling for the effects of baseline covariates, including age (<40 years, 40 to 49 years, and >49 years), race or ethnicity (white, African American, Latino, or other), protease inhibitor, viral load detectability on day 0, small or large RNA change during the lead-in period (≤0.5 versus >0.5 $\log_{10}$ copies/mL), and baseline $\log_{10}$ $CD4^+$ and $\log_{10}$ $CD8^+$ cell counts. Similarly, we modeled $\log_{10}$ HIV RNA levels at day 0 and all eight follow-up time points, using a random intercept repeated-measures model. This model allowed baseline covariates to modify either the intercept or the slope and included a quadratic time trend for patients with large RNA changes during the lead-in period. This subgroup showed marked benefit from participation in the clinical trial during the lead-in period and early part of the follow-up period; their RNA levels were typical of all study participants. The simpler model compared HIV RNA levels at the start and end of the trial (two levels per participant), whereas the repeated-measures model used nine levels per participant to estimate the changes from day 0 to day 21; therefore, the latter cannabinoid effect estimates were less influenced by measurement error at any one time point. Because we were concerned about violations of model assumptions of normality and homoscedasticity, all CIs and *P* values reported were calculated by using the bias-corrected, accelerated bootstrap method with participant-level resampling and 2000 bootstrap iterations (38). These are valid even when the assumptions are violated. Finally, each model was examined for the effects of influential observations, identified through the algorithm of Lesaffre and Verbeke (39).

The cannabinoid groups also were compared with the placebo group with respect to changes in $CD4^+$ and $CD8^+$ cell counts, adjusted for the covariates above and for baseline HIV RNA level. The model of $CD4^+$ cell

Figure 1. **Flow of participants through the randomized trial.**



THC = tetrahydrocannabinol.

counts was additionally adjusted for baseline $CD8^+$ counts and vice versa. We added 10 to the cell counts to reduce the influence of very small values and then transformed to the $\log_{10}$ scale to ensure model validity. These models estimate multiplicative effects on geometric means, which we described as percentage effects by converting the effect on the original log scale with the formula $(10^{\text{effect}} - 1) \times 100\%$. For example, an effect of 0.05 is a 12% greater increase in cell count for a cannabinoid than a placebo participant with the same initial count, regardless of whether it was 0.005 or 0.5×10^9 cells/L. We used medians and ranges to describe within-group changes in body weight over the study period and Mann–Whitney tests to compare the cannabinoid and placebo groups. All *P* values reported are two-sided.

To investigate the effect of imputing a single fixed value of 49 copies/mL for undetectable viral loads, we used the SAS Lifereg procedure (SAS Institute, Inc., Cary, North Carolina) to instead treat undetectable viral loads as left-censored at the detection limit. Although this method is usually used for survival time analysis, we obtained the needed models by using viral load as the time variable and specifying a log-normal distribution.

Role of the Funding Source

The funding source reviewed and funded the protocol and provided the marijuana cigarettes for the trial.

RESULTS

Characteristics of Patients

A total of 603 individuals volunteered for the study, but most did not meet the eligibility criteria (**Figure 1**). Of the 69 study participants admitted to the inpatient study unit, 67 were randomly assigned between May 1998 and May 2000. Thirty-seven patients were receiving nelfinavir-containing regimens and 30 patients were receiving indinavir-containing regimens. Of these, 3 and 2 patients, respectively, left the study before the pharmacokinetic analysis on day 14. The remaining 62 study participants completed the 21-day inpatient intervention phase and were eligible for all end points (marijuana group, 20 patients; dronabinol group, 22 patients; and placebo group, 20 patients).

Most patients were men (89%) older than 40 years of age (68%), and half were of nonwhite ethnicity (**Table 1**). More patients in the marijuana and dronabinol groups

than in the placebo group had previous AIDS diagnoses and detectable HIV RNA than in the placebo group. Overall, 58% of the participants had undetectable HIV RNA levels (<50 copies/mL); only 5 patients had HIV RNA levels greater than 10 000 copies/mL, 4 of whom were receiving nelfinavir-containing regimens. Baseline $CD4^+$ and $CD8^+$ cell counts were similar in all groups.

During the 4-day lead-in phase, no participant's HIV RNA level increased by 0.5 $\log_{10}$ copies/mL (3.2-fold). However, HIV RNA levels decreased by at least this amount in 5 patients (marijuana group, 3 patients; dronabinol group, 2 patients; placebo group, 0 patients): 1 of 28 patients receiving indinavir, 1 of 13 patients receiving nelfinavir three times daily, and 3 of 21 patients originally receiving nelfinavir twice daily. Changing the nelfinavir regimen from two to three doses per day seemed to have a large effect on HIV RNA levels. However, since large decreases in HIV RNA occurred in participants receiving all three regimens, they also might be due to the fact that therapy was directly observed.

Change in HIV RNA Levels

HIV RNA was undetectable at days 0 and 21 in 50% to 55% of patients in each group (**Table 2**). Although the median change in each group was 0, the mean changes were decreases in both cannabinoid groups: marijuana group, −0.14 $\log_{10}$ copies/mL (95% CI, −0.42 to 0.03 $\log_{10}$ copies/mL), and dronabinol group, −0.18 $\log_{10}$ copies/mL (CI, −0.51 to −0.04 $\log_{10}$ copies/mL). These findings were due mainly to five study participants with 0.5 $\log_{10}$ copies/mL or greater decreases in viral load during follow-up. The mean change among patients receiving placebo, 0.06 $\log_{10}$ copies/mL (CI, −0.03 to 0.24 $\log_{10}$ copies/mL), was an increase, and no patient experienced a large decrease during follow-up. The unadjusted mean change in the marijuana group was −0.19 $\log_{10}$ copies/mL (CI, −0.48 to 0.01 $\log_{10}$ copies/mL) lower than in the placebo group, and the corresponding mean difference between the dronabinol and placebo groups was −0.24 $\log_{10}$ copies/mL (CI, −0.55 to −0.06 $\log_{10}$ copies/mL). After we controlled for the large change in HIV RNA level during the lead-in period (≤0.5 vs. >0.5 $\log_{10}$ decrease) and other covariates previously mentioned, the mean marijuana–placebo difference was −0.06 $\log_{10}$ copies/mL (CI, −0.26 to 0.13 $\log_{10}$ copies/mL) and the mean dronabinol–placebo difference was −0.07 $\log_{10}$ copies/mL (CI, −0.24 to 0.06 $\log_{10}$ copies/mL). Models treating undetectable viral loads as left-censored produced slightly higher upper confidence bounds of 0.23 for the marijuana–placebo difference and 0.09 for the dronabinol–placebo difference.

The repeated-measures models of nine measurements per study participant seemed to fit adequately with only linear terms for treatment effects over time, since quadratic terms did not approach statistical significance. A quadratic term was needed only for the five patients with large change in HIV RNA level during the lead-in period. Before adjustment, the cannabinoids seemed to reduce viral load, whereas after adjustment they seemed to have little effect on this outcome. In particular, on the basis of the adjusted model, both upper confidence bounds for the treatment effects (marijuana group, 0.13 [34%]; dronabinol group, 0.14 [37%]) excluded cannabinoid-associated

Table 1. **Baseline Characteristics***

Characteristic	Marijuana Group (*n* = 20)	Dronabinol Group (*n* = 22)	Placebo Group (*n* = 20)	All Groups (*n* = 62)
Median age (range), *y*	41.5 (33–54)	43 (34–52)	44.5 (26–80)	43 (26–80)
Sex, *n (%)*				
Men	17 (85)	19 (86)	19 (95)	55 (89)
Women	2 (10)	1 (5)	0 (0)	3 (5)
Transgender (male-to-female)	1 (5)	2 (9)	1 (5)	4 (6)
Race or ethnicity, *n (%)*				
White	13 (65)	9 (41)	9 (45)	31 (50)
African American	3 (15)	6 (27)	3 (15)	12 (19)
Latino or Latina	1 (5)	4 (18)	5 (25)	10 (16)
Other	3 (15)	3 (14)	3 (15)	9 (15)
Median body mass index (range), kg/m^2	25.6 (21.9–53.3)	25.0 (14.8–38.2)	25.4 (18.7–33.0)	25.5 (14.8–53.3)
Use of protease inhibitor, *n (%)*				
Nelfinavir	11 (55)	12 (55)	11 (55)	34 (55)
Indinavir	9 (45)	10 (45)	9 (45)	28 (45)
Previous opportunistic infection or malignant condition, *n (%)*	12 (60)	12 (55)	6 (30)	30 (48)
Median HIV RNA level (range), log_{10} *copies/mL*	3.5 (2.0–4.5)	3.5 (1.7–4.3)	3.7 (1.8–4.6)	3.6 (1.7–4.6)
Undetectable HIV RNA levels, *n (%)*	12 (60)	11 (50)	13 (45)	36 (58)
Median $CD4^+$ cell count (range), $\times 10^9$ *cells/L*†	0.345 (0.026–0.9)	0.315 (0.052–0.771)	0.378 (0.007–0.906)	0.34 (0.007–0.906)
$CD4^+$ cell count < 200 × 10^9 cells/L, *n (%)*	5 (25)	5 (24)	5 (28)	15 (24)
Median $CD8^+$ cell count (range), $\times 10^9$ *cells/L*†	0.736 (0.433–1.987)	0.91 (0.223–2.23)	0.708 (0.3–1.987)	0.757 (0.223–2.23)

* Among patients with baseline viral load levels > 50 copies/mL.
† Three patients had missing data for $CD4^+$ and $CD8^+$ cell counts on day 0: dronabinol group, 1 patient, and placebo group, 2 patients.

Table 2. **Changes in Viral Load Level by Group**

Variable	Marijuana Group ($n = 20$)	Dronabinol Group ($n = 22$)	Placebo Group ($n = 20$)
Change between day 0 and day 21 (2 time points), *n (%)*			
Increase > 0.5 $\log_{10}$ copies/mL	1 (5)	0 (0)	1 (5)
Increase ≥ 0.5 $\log_{10}$ copies/mL	4 (20)	2 (9)	5 (25)
Decrease < 0.5 $\log_{10}$ copies/mL	2 (10)	7 (32)	3 (15)
Decrease ≥ 0.5 $\log_{10}$ copies/mL	3 (15)	2 (9)	0 (0)
No change	10 (50)	11 (50)	11 (55)
Unadjusted mean difference in viral load from placebo group (95% CI), *$\log_{10}$ copies/mL*	−0.19 (−0.48 to 0.01)*	−0.24 (−0.55 to −0.06)†	—
Adjusted mean difference in viral load from placebo group (95% CI)‡, *$\log_{10}$ copies/mL*	−0.06 (−0.26 to 0.13)§	−0.07 (−0.24 to 0.06)§	—
Average change in viral load at day 21 (repeated measures: 9 time points), *$\log_{10}$ copies/mL*			
Adjusted mean difference in viral load from placebo group (95% CI)‖	−0.07 (−0.30 to 0.13)§	−0.04 (−0.20 to 0.14)§	—

* $P = 0.07$.
† $P < 0.001$.
‡ Multivariable models were adjusted for the following covariates: age, race, protease inhibitor, viral load detectability at day 0, small or large viral load change during the lead-in period, baseline $\log_{10}$ $CD4^+$ cell counts, and $\log_{10}$ $CD8^+$ cell counts. Three patients who were missing data on baseline $CD4^+$ and $CD8^+$ cell counts were excluded from multivariate models. The models yielded results similar to those of the models that included all independent variables and led to the same conclusions.
§ $P > 0.2$.
‖ In addition to the covariates listed, this model controlled for a quadratic time effect among patients with large viral load change during the lead-in period.

increases in viral load of 0.3 $\log_{10}$ copies/mL (100%), our a priori threshold for concern.

Change in $CD4^+$ and $CD8^+$ Cell Subsets

Figure 2 shows the median changes in absolute numbers of $CD4^+$ and $CD8^+$ cells over the 21-day experimental intervention. Compared with patients receiving placebo, the unadjusted mean increases in $CD4^+$ cell counts were greater for patients receiving cannabinoids than for patients receiving placebo (marijuana group, 20% [CI, 7% to 55%]; dronabinol group, 17% [CI, 5% to 45%]) (**Table 3**). The adjusted two-point model and the repeated-measures model showed similar findings.

Over the 21-day follow-up period, increases in $CD8^+$ cell counts were on average 20% (CI, 7% to 38%) greater for patients receiving marijuana than for patients receiving placebo and marginally greater (10% [CI, −5% to 29%]) for patients receiving dronabinol than for those receiving placebo. In the adjusted repeated-measures model, the cannabinoid effects were similar (lower confidence bounds: marijuana group, 4%; dronabinol group, −3%). An analysis of expanded immune system phenotypes and functions revealed few statistically significant effects (40).

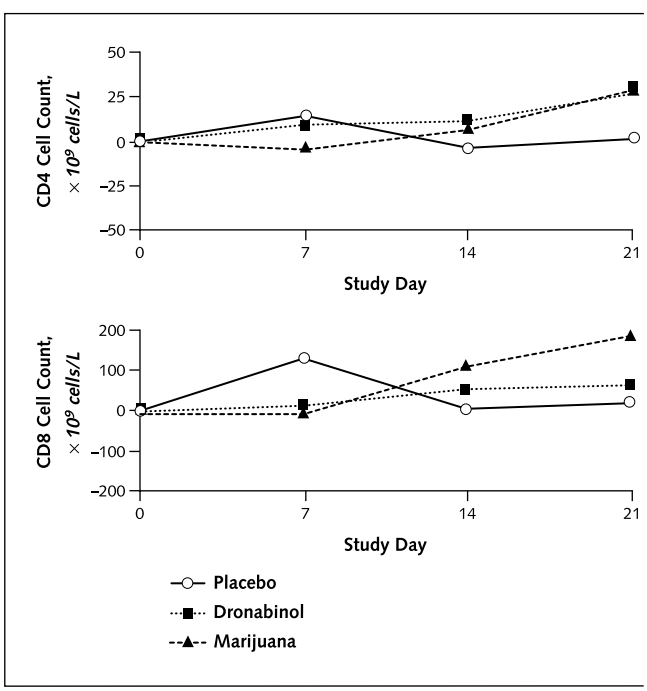
Pharmacokinetics

The detailed results of the effects of the cannabinoids on the pharmacokinetics of the protease inhibitors have been described elsewhere (35, 41). No clinically significant alterations of nelfinavir or indinavir levels were noted.

Change in Weight

Although safety was the primary end point of this trial, study participants underwent many evaluations to assess the effect of cannabinoids on appetite, caloric intake, weight, and body composition. Over the 21-day study period, the placebo recipients gained a median of 1.1 kg (range, −1.4 to 5.2 kg). The participants in the marijuana and dronabinol groups gained significantly more weight, a median of 3.0 kg (range, −0.75 to 8.6 kg; $P = 0.021$) and 3.2 kg (range, −1.4 to 7.6 kg; $P = 0.004$), respectively. Dual-energy x-ray absorptiometry demonstrated that most of the weight gained in all groups was fat mass (42).

Figure 2. **Changes in $CD4^+$ and $CD8^+$ cell counts by group ($n = 62$).**



Top. Median change in $CD4^+$ cell counts over the 21-day study period. **Bottom.** Median change in $CD8^+$ cell counts over the 21-day study period.

Table 3. **Changes in $CD4^+$ and $CD8^+$ Cell Counts Relative to the Placebo Group***

Variable	Marijuana Group (n = 20)	Dronabinol Group (n = 21)
Relative change in $CD4^+$ cell count between day 0 and day 21 (2 time points)		
Unadjusted estimated effect, %	20 (7 to 55)	17 (5 to 45)
P value	<0.001	<0.001
Adjusted estimated effect, %†	13 (−1 to 28)	12 (−2 to 28)
P value	0.06	0.09
Relative change in $CD4^+$ cell count at day 21 (repeated measures: 4 time points)		
Adjusted estimated effect, %†	16 (2 to 33)	14 (−1 to 32)
P value	0.025	0.064
Relative change in $CD8^+$ cell count between day 0 and day 21 (2 time points)		
Unadjusted estimated effect, %	20 (7 to 38)	10 (−5 to 29)
P value	0.002	>0.2
Adjusted estimated effect, %†	16 (2 to 36)	8 (−5 to 27)
Relative change in $CD8^+$ cell count at day 21 (repeated measures: 4 time points)		
Adjusted estimated effect, %†	20 (4 to 42)	10 (−3 to 32)
P value	0.016	0.15

* The placebo group included 18 participants. All values in parentheses are 95% CIs.

† Multivariable models included the following covariates: age; race; protease inhibitor; viral load detectability at day 0; small or large viral load change during the lead-in period; baseline $\log_{10}$ HIV RNA level; and baseline $\log_{10}$ $CD8^+$ and $\log_{10}$ $CD4^+$ cell counts for $\log_{10}$ $CD4^+$ and $\log_{10}$ $CD8^+$ cell models, respectively. The models yielded results similar to those of the models that included all independent variables and led to the same conclusions.

DISCUSSION

This study provides evidence that short-term use of cannabinoids, either oral or smoked, does not substantially elevate viral load in individuals with HIV infection who are receiving stable antiretroviral regimens containing nelfinavir or indinavir. Upper confidence bounds for all estimated effects of cannabinoids on HIV RNA level from all analyses were no greater than an increase of 0.23 $\log_{10}$ copies/mL compared with placebo. Because this study was randomized and analyses were controlled for all known potential confounders, it is very unlikely that chance imbalance on any known or unknown covariate masked a harmful effect of cannabinoids. Study participants in all groups may have been expected to benefit from the equivalent of directly observed antiretroviral therapy, as well as decreased stress and, for some, improved nutrition over the 25-day inpatient stay.

Neither $CD4^+$ nor $CD8^+$ cell counts seemed to be adversely affected by the cannabinoids during the study; lower confidence bounds on estimated cannabinoid effects typically exceeded 0, indicating benefit rather than harm. Increases in $CD8^+$ cell counts in the marijuana group seen in our study differ from findings reported in earlier studies conducted in participants without HIV infection (29). The clinical significance and mechanism accounting for these changes are unclear.

The pharmacokinetic component of this study did not demonstrate clinically significant interactions with cannabinoids that would warrant dose adjustments of protease inhibitors in the context of smoked marijuana or dronabinol use (35). However, given the great variability of the pharmacokinetics of protease inhibitors, the long-term significance of the short-term concentration decreases observed is not known.

Although the primary objective of this study was to assess the safety of cannabinoids in patients with HIV infection treated with protease inhibitor–containing antiretroviral regimens, a secondary aim was to obtain some information on activity, particularly about appetite stimulation and weight gain. Whereas previous studies of dronabinol have demonstrated significantly increased appetite and only a trend toward weight gain, this trial shows increased weight in both cannabinoid groups compared with the placebo group. However, the weight gained by the cannabinoid recipients was not in the desired lean body mass but in fat.

Our conclusions are limited by the short duration of this study. Also, few women participated, so our results may apply mainly to men. The results of this study, which evaluated government-supplied marijuana of known potency and content, cannot be extrapolated to the potential effects of marijuana available on the street. In addition, the lack of a blinded control group for the smoked marijuana arm could bias the interpretation of some of our results, such as the weight changes; however, it is difficult to attribute effects on HIV RNA level and $CD4^+$ and $CD8^+$ cell counts to any such potential bias. We chose not to include a smoked placebo group because we thought it would be impossible to blind marijuana in study participants with previous marijuana experience. Of interest, most of the patients receiving dronabinol (17 of 22) could identify their blinded treatment correctly, whereas the patients in the placebo group had more difficulty (9 of 20). This suggests that placebo-controlled studies of the efficacy of smoked marijuana could be considered in the future.

The Institute of Medicine reviewed accumulated data on the safety and effectiveness of marijuana as medicine in a recent comprehensive report (43). The discussion of medicinal marijuana is a polarizing one that is confounded by emotion and politics, usually unsupported by data. Our short-duration clinical trial suggests acceptable safety in a vulnerable immune-compromised patient population. Further studies investigating the therapeutic potential of marijuana and other cannabinoids in patients with HIV infection and other populations are ongoing and should provide additional safety information over longer exposure periods (44).

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Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

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Abstract—*Objective:* To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model. *Methods:* Prospective randomized placebo-controlled trial conducted in the inpatient General Clinical Research Center between May 2003 and May 2005 involving adults with painful HIV-associated sensory neuropathy. Patients were randomly assigned to smoke either cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Primary outcome measures included ratings of chronic pain and the percentage achieving >30% reduction in pain intensity. Acute analgesic and anti-hyperalgesic effects of smoked cannabis were assessed using a cutaneous heat stimulation procedure and the heat/capsaicin sensitization model. *Results:* Fifty patients completed the entire trial. Smoked cannabis reduced daily pain by 34% (median reduction; IQR = −71, −16) vs 17% (IQR = −29, 8) with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($p \leq 0.05$) but appeared to have little effect on the painfulness of noxious heat stimulation. No serious adverse events were reported. *Conclusion:* Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

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HIV-associated sensory neuropathy (HIV-SN) is the most common peripheral nerve disorder complicating HIV-1 (HIV) infection.[1-3] The dominant symptom in HIV-SN is pain, most often described as "aching," "painful numbness," or "burning." Hyperalgesia and allodynia are common, while weakness is rare and usually confined to the intrinsic foot muscles.

Anticonvulsant drugs have been shown to be effective, specifically lamotrigine and gabapentin, but some patients fail to respond or cannot tolerate these agents.[4,5] Adverse drug-drug interactions with antiretrovirals limit the utility of other antiepileptic drugs used for neuropathic pain, such as carbamazepine.[6] Peptide T, mexiletine, acupuncture, and capsaicin cream were no more effective than placebo in relieving pain from HIV-SN.[7-11] Similarly, tricyclic antidepressants also were no more beneficial than placebo in relieving pain in controlled trials for HIV-SN.[9,10]

Extensive preclinical research has demonstrated analgesic effects of exogenous cannabinoids as well as an endogenous cannabinoid system involved in pain and analgesia.[12,13] The need for a greater variety of effective therapeutic options has led to heightened interest in evaluating smoked cannabis as a treatment for chronic neuropathic pain. Incorporating an experimental pain model into the assessment of smoked cannabis in patients with chronic pain from HIV-SN provides a standardized reference point for each patient's subjective ratings of ongoing chronic pain. The Long Thermal Stimulation procedure tests for acute analgesia by measuring the painfulness of a 1-minute heat stimulus.[14] The heat/capsaicin sensitization model tests for anti-hyperalgesic effects.[15] By simultaneously evaluating acute experimentally induced pain and hyperalgesia and ongoing neuropathic pain, we sought to determine the effect of smoked cannabis on the neuropathic pain of HIV-SN, and to determine if cannabinoids have a more general analgesic and anti-hyperalgesic effect.

Methods. *Study patients.* Patients were adults with HIV infection and symptomatic HIV-SN with an average daily pain score of

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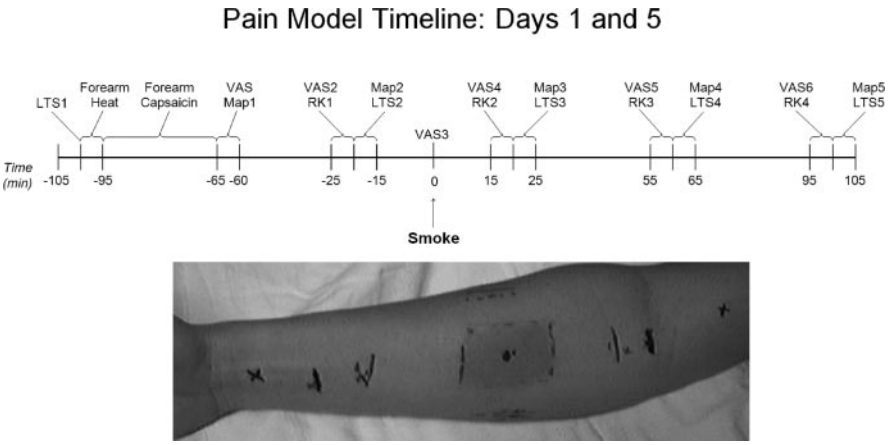

Figure 1. Timeline of procedures associated with first and last smoking sessions (day 1 and day 5) and illustration of marking of borders of hyperalgesia on the forearm surrounding the stimulated area. Procedures: LTS = long thermal stimulation—upper arm (45 °C for 1 minute); forearm heat: 45 °C for 5 minutes; forearm capsaicin: 0.075% for 30 minutes; VAS = Visual Analog Scale—Rating of current neuropathic pain; map = map area of secondary hyperalgesia (brush and von Frey); RK = rekindling—forearm (40 °C for 5 minutes).

at least 30 mm on the 100 mm visual analog scale during the outpatient pre-intervention phase. Patients were in stable health, were without current substance abuse (including tobacco), and followed a stable medication regimen for pain and HIV for at least 8 weeks prior to enrollment. Painful HIV-SN was confirmed by symptoms of symmetric distal pain or dysesthesias in the lower extremities for at least 2 weeks, combined with absent or depressed ankle reflexes or sensory loss of vibration, pin, temperature, or touch on examination by the study neurologist (C.A.J.). A family history of polyneuropathy, neuropathy due to causes other than HIV or dideoxynucleosides, and use of isoniazid, dapsone, or metronidazole within 8 weeks prior to enrollment were exclusionary. HIV neuropathy was defined as onset of symptoms without concomitant dideoxynucleoside antiretroviral therapy and nucleoside neuropathy as symptom onset during dideoxynucleoside treatment. Subjects with HIV neuropathy whose symptoms worsened on dideoxynucleoside agents were considered to have both HIV and nucleoside neuropathy.

All patients were required to have prior experience smoking cannabis (defined as six or more times in their lifetime), so that they would know how to inhale and what neuropsychologic effects to expect. Current users were asked to discontinue any cannabis use prior to study admission.

The study was approved by the Institutional Review Board at the University of California San Francisco, the Research Advisory Panel of California, the Drug Enforcement Administration, the Food and Drug Administration, and the National Institute on Drug Abuse. Written informed consent was obtained from all patients. The trial was monitored by an independent Data Safety Monitoring Board (DSMB) established by the University of California Center for Medicinal Cannabis Research.

Study medication. The National Institute on Drug Abuse provided identically appearing pre-rolled cannabis and placebo cigarettes weighing on average 0.9 g. Active cannabis cigarettes contained 3.56% delta-9-tetrahydrocannabinol (delta-9-THC), and identical-appearing placebo cannabis cigarettes from which the active components had been extracted contained 0% delta-9-THC. The cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the San Francisco General Hospital General Clinical Research Center where the inpatient study was conducted. The frozen cigarettes were rehydrated overnight in a humidifier. Patients were housed in a room with a fan ventilating to the outside. Research staff monitored patients during smoking sessions, weighed the cannabis cigarettes immediately before and after they were administered to patients, and returned all leftover material to the pharmacy. To maximize standardization of inhaled doses, patients followed a uniform puff procedure.[16]

Study timeline and procedures. The study had four phases: a 7-day outpatient pre-intervention phase (study days –9 to –3) to establish eligibility; a 2-day inpatient lead-in phase (study days –2 and –1) in which patients were acclimated to the inpatient General Clinical Research Center setting and baseline measurements were obtained; a 5-day inpatient intervention phase (study days 1 to 5); and a 7-day outpatient post-intervention phase (study days 6 to 12) during which patients continued to record pain ratings each day.

Randomization (1:1) to cannabis or placebo cigarettes was computer-generated by the study statistician and managed by an independent research pharmacist. Treatment was double-blind. After hospital admission on day –2, patients were not allowed to leave the hospital or receive visitors. Patients smoked their first cigarette at 2 PM on day 1, and their last cigarette at 2 PM on day 5. Pain model procedures and repeated ratings of chronic pain were incorporated into the first and last smoking session, as shown in figure 1. On the intervening study days, patients smoked, as tolerated, one cigarette three times daily (8:00 AM, 2:00 PM, 8:00 PM). Preadmission analgesics were continued throughout the study.

Primary outcome measure: Daily diary pain VAS. Beginning with the outpatient pre-intervention phase and extending through the post-intervention phase, patients completed a diary at 8 AM each morning to rate their chronic neuropathic pain during the preceding 24 hours on a 100 mm visual analog scale (VAS) labeled "no pain" at 0 mm and "worst pain imaginable" at 100 mm.

Secondary outcome measures: Day 1 and day 5 smoking sessions. Ratings of chronic neuropathic pain VAS. To assess the immediate effect of smoked cannabis on chronic neuropathic pain, patients rated their current pain at 40-minute intervals three times before and three times after smoking the first and last cigarette on a 100-mm VAS (figure 1). In the pilot study, we observed rapid increases in plasma levels of delta-9 THC after 2 minutes (mean = 96.8 ng/mL; 95% CI = 48.7, 145.0) with rapid declines after 1 hour (mean = 6.2 ng/mL; 95% CI = 3.3, 9.2). This study was designed so these measures were collected within the time of peak plasma levels.

LTS procedure. The long thermal stimulation procedure (LTS) was used to assess acute analgesic effects. Skin on the non-dominant shoulder was heated using a computer-controlled Peltier device with a 15.7-cm^2 surface area thermode (TSA 2001, Medoc, Israel).[17,18] The probe is held against the skin at a holding temperature of 32 °C and then heated to 45 °C at a linear rate. On reaching 45 °C, pain is then rated continuously using an electronic visual analog scale with a 100-mm linear track for 1 minute before thermode removal. The LTS procedure was performed twice before and three times after smoking.

Heat/capsaicin sensitization model. The heat/capsaicin sensitization model was used to assess anti-hyperalgesic effects by inducing neuronal sensitization sufficient to produce an area of cutaneous secondary hyperalgesia that can be mapped and quantified.[14,15,17-19] Heat/capsaicin sensitization was induced on a 22.8 cm^2 stimulation site on the forearm by using the thermode to heat the skin to 45 °C for 5 minutes followed by treating the stimulation site with topical capsaicin cream (0.075%, Capzaisin HP, Chattem Inc.; Chattanooga, TN) for 30 minutes. Cutaneous hyperalgesia was maintained by heating the stimulation site to 40 °C for 5 minutes (rekindling procedure) at 40-minute intervals. After each rekindling, areas of secondary hyperalgesia were quantified with a 1-inch foam brush and with a 26-g von Frey hair (a mildly noxious pin-like sensation) by stimulating along linear rostral–caudal and lateral–medial paths around the stimulation site in 5-mm steps at 1-second intervals. Starting well outside the hyperalgesic area and continuing toward the treated skin area, the skin was marked where patients reported a definite change in

sensation (such as burning, tenderness, or more intense pricking). The distances from the center of the stimulation site were then measured and surface area calculated. The first (baseline) rekindling was performed before smoking and rekindling was repeated three times after smoking.

Safety, side effects, and mood ratings. On study days –1, 2, and 5, patients completed the Profile of Mood States to assess total mood disturbance and subscales of tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.[20] Side effects of anxiety, sedation, disorientation, paranoia, confusion, dizziness, and nausea were patient-rated on a 0 to 3 scale (none, mild, moderate, severe) at 9:00 AM, 3:00 PM, and 9:00 PM during the entire hospital stay. Adverse events were graded using the NIH Division of AIDS table for grading severity of adult adverse experiences.[21]

Statistical analysis. Study sample size was based on an open-label pilot trial in 16 patients with HIV-SN of very similar design.[22] The mean reduction in pain was 30.1% (95% CI: −61.2, 1.0). Ten pilot patients (62%) had a greater than 30% decrease in their daily pain, the prespecified criterion of clinically meaningful pain relief.[23] Applying the same variances to a randomized, placebo-controlled trial and conservatively estimating that 50% of cannabis patients and 13% of placebo patients would meet the 30% pain reduction criterion yields a sample size of 48 patients with an alpha of 0.05 and a beta of 0.20.

Statistical analyses were conducted on a modified intent-to-treat (ITT) sample. All patients who remained in the study at each time point were included in the analyses. The primary outcome was the proportion of patients in the cannabis and placebo groups who experienced at least a 30% reduction in daily diary pain level from baseline (average of the two daily diary pain levels rated at 8 AM on study day −1 and study day 1) to end-of-treatment (average of study days 4 and 5). p Values were obtained using χ^2 test for 2 by 2 tables.

The co-primary outcome variable was the percent change in pain from baseline. Percent change in each group was not normally distributed; therefore, the nonparametric Mann-Whitney test was used to compare percent change in pain across study groups. Pain reduction was also modeled as a function of group and time using a repeated measures model (generalized estimating equations). All available patient information, including information on patients who later withdrew from the study, was included in this model. The data were fitted using time squared to allow for non-linearity in the relationship between group and time. To adjust for potentially confounding patient characteristics, we controlled for age, gender, pre-study ongoing use of cannabis (yes or no), cause of neuropathy, and baseline daily pain.

Secondary outcome variables collected while smoking the first cigarette on day 1 and the last cigarette on day 5 consisted of percent change (relative to pre-smoking baseline for that session) in 100 mm VAS ratings of chronic neuropathic pain, painfulness of the LTS procedure, and areas of secondary hyperalgesia produced by the heat/capsaicin sensitization model to brush and von Frey hair stimuli. For each of these repeated measures, the area under the curve (AUC) for percent change in pain or area of sensitization was computed relative to pre-smoking baseline values (or the average of the pre-smoking values if multiple measurements were available). The total AUC was standardized as average percent change per hour by dividing each AUC by 60. Differences in AUC were compared using Mann-Whitney tests as these data were not normally distributed.

Additional secondary outcome analyses of the percent change in total mood disturbance and percent change in the six subscales of the Profile of Mood States was analyzed using independent t tests or Mann-Whitney tests if the data were not normally distributed. Side effect ratings were compared using repeated measures models (generalized estimating equations), using a negative binomial distribution to allow for rare events and over-dispersed data and adjusted for differences in mean recorded side effects across study days and time of day of measurement.

Role of the funding source. The University of California Center for Medicinal Cannabis Research provided assistance with obtaining necessary regulatory approvals, data quality monitoring, and establishing the study's Data Safety Monitoring Board.

Results. *Study patients.* A total of 223 patients were assessed for eligibility between May 2003 and May 2005

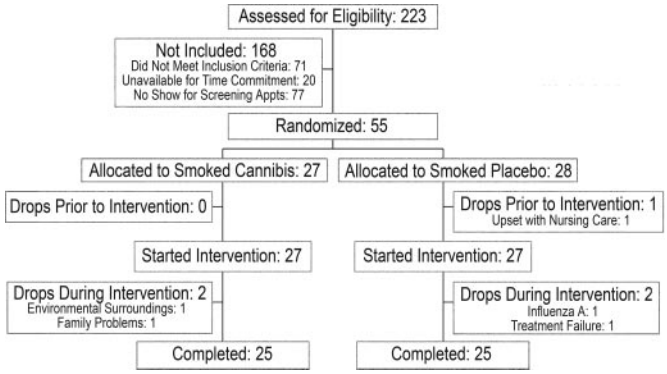

Figure 2. Flow of participants through the trial.

(figure 2) and 55 individuals were enrolled. Of these, 27 were randomized to cannabis cigarettes and 28 were randomized to placebo cigarettes. One patient withdrew during the inpatient intervention phase prior to smoking the first cigarette, and four additional patients withdrew prior to completion of the inpatient phase, leaving 25 patients in each group who completed the entire study. All smoking sessions were observed by research staff and completed per protocol.

Thirty randomized patients completed the experimental pain model portion of the study (14 cannabis, 16 placebo). Of the 25 patients who did not fully participate in this portion of the study, 17 could not tolerate the painful stimulation when tested during the outpatient pre-intervention phase, one developed a blister, one discontinued prior to study day 1, and six did not meet eligibility criteria for the pain model portion (extensive tattooing in one and heat pain detection threshold above 47 °C in five).

The patients randomized to cannabis and placebo cigarettes were similar with regard to demographic and baseline characteristics (table 1). Patients were predominantly men with 14 years of HIV infection and 7 years of peripheral neuropathy. Neuropathy was believed to be secondary to antiretroviral medications in the majority of patients in both groups. Over half of patients in each group used concomitant medications for pain, with about one quarter of each group using more than one type of concomitant medication. The most frequently used concomitant medication was gabapentin (15 patients) followed by opioids (14 patients).

Primary outcome measure. Median daily pain ratings for the two groups throughout the entire study are shown in figure 3. Baseline (average of day −1 and day 1) daily diary pain ratings were similar (cannabis median 52, interquartile range [IQR] = 38, 71; placebo median 57, IQR = 40, 74). Among those who completed the study, 13 of 25 patients randomized to cannabis cigarettes had >30% reduction in pain from baseline to end of treatment vs 6 of 25 patients receiving placebo cigarettes (52% vs 24%; difference 28%, 95% CI 2% to 54%, $p = 0.04$). The median reduction in chronic neuropathic pain on the daily diary VAS was 34% (IQR = −71, −16) in the cannabis group and 17% in the placebo group (IQR = −29, 8; difference = 18%; $p = 0.03$, Mann-Whitney test). In the multivariable repeated measures model, which analyzed available data from all randomized patients, the estimated group difference was slightly larger than the observed dif-

Table 1 *Patient characteristics*

Sex, n (%)*	Cannabis (n = 27)	Placebo (n = 28)
Male	22 (81)	26 (93)
Female	5 (19)	2 (7)
Age, y, mean ± SD	50 ± 6	47 ± 7
Race/ethnicity, n (%)		
White	14 (52)	11 (39)
African American	9 (33)	12 (43)
Latino	3 (11)	5 (18)
Asian/Pacific Islander	1 (4)	0
Duration of HIV, y, mean ± SD	15 ± 4	14 ± 5
On HAART, n (%)	18 (67)	24 (86)
CD4+ T lymphocyte (cells/mm^3), median (IQR)	355 (250, 536)	444 (311, 523)
Viral load, n (%)		
<400	19 (70)	17 (61)
≥400	8 (30)	11 (39)
Duration of neuropathy, y, median (IQR)	7 (3, 9)	7 (3, 9)
Cause of neuropathy, n (%)		
HIV	10 (37)	7 (25)
Nucleosides	12 (44)	14 (50)
Both	5 (19)	7 (25)
Intensity of pain at baseline (0–100), mean ± SD	53 ± 20	54 ± 23
Current cannabis use, n (%)		
Yes	21 (78)	19 (68)
No	6 (22)	9 (32)
Concomitant medications, n (%)	15 (56)	16 (57)
Types of concomitant medications, n (%)†		
Gabapentin	7 (26)	7 (25)
Opioid	5 (19)	8 (29)
Other medication	9 (33)	10 (36)
Multiple concomitant medications, n (%)	6 (22)	7 (25)

* Male to female transgender for 1 cannabis and 2 placebo patients.
† Multiple responses possible.

ference among those who completed the study (26%; 95% CI = 0, 51; $p = 0.05$).

Secondary outcome measures. Smoking the first cannabis cigarette reduced chronic pain ratings (AUC) by a median of 72% vs a reduction of 15% with placebo cigarettes ($p < 0.001$, Mann-Whitney test; figure 4A). On day 5 just prior to smoking the last cigarette, median ratings of current chronic pain intensity were lower in the cannabis group (15; IQR = 7, 34) than in the placebo group (29; IQR = 20, 60; $p = 0.006$, Mann-Whitney test). Smoking the last cigarette further reduced chronic pain ratings 51% in the cannabis group vs 5% in the placebo group ($p < 0.001$, Mann-Whitney test).

In the 30 patients who underwent the pain model portion of the study, LTS (a measure of acute analgesia to noxious heat stimuli) did not appear to be substantially reduced by smoking the first cigarette on day 1 in either group (figure 4B, median = −22% for cannabis and −5% for placebo; $p = 0.31$). Areas of experimental heat/capsaicin secondary hyperalgesia on the forearm were similar in the two groups prior to smoking the first cigarette. Active cannabis reduced the area to both brush and von Frey hair stimuli compared to placebo (median = −34% vs −11%; $p = 0.05$ and −52% vs + 3%; $p = 0.05$; figure 4, C and D). Smoking the last cigarette on day 5 did not alter the painfulness of the LTS procedure or reduce the areas of secondary hyperalgesia in either group.

Safety and mood effects of cannabis. No patient withdrew from the study because of adverse events. One episode of grade 3 dizziness related to study medication occurred in the cannabis group. One case of transient grade 3 anxiety possibly related to study medication was reported in each group. Both patients received a one-time dose of lorazepam. No other patients required psychotropic medications for treatment of dysphoric effects. No episodes of hypertension, hypotension, or tachycardia requiring medical intervention occurred.

Mean recorded side effects were low in both study groups. However, side effects ratings were higher in patients in the cannabis group, as shown in table 2, for anx-

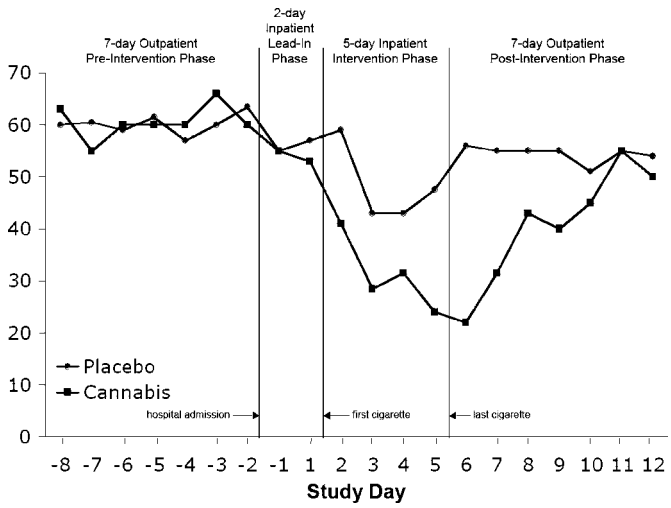

Figure 3. Time course of the intensity of chronic neuropathic pain as rated on the daily diary VAS at 8 AM for the previous 24-hour period. Each point represents the group median. Study admission was at noon on study day –2, the first cigarette was smoked at 2 PM on study day 1, and the last cigarette was smoked at 2 PM on study day 5.

iety ($p = 0.04$), sedation ($p < 0.001$), disorientation ($p < 0.001$), confusion ($p < 0.001$), and dizziness ($p < 0.001$). Although these differences were significant, the values for both groups hovered closer to zero than one and do not represent any serious safety concerns in this short-term study. The Profile of Mood States indicated a reduction in total mood disturbance during the 5 days of smoking (median −33% cannabis vs −29% placebo; $p = 0.28$). Although all subscale scores declined in both groups, the only difference was a larger decrease in depression-dejection in the placebo group (median −63% cannabis vs −76% placebo; $p = 0.05$, Mann-Whitney test).

Discussion. Over a 5-day inpatient intervention period, smoking cannabis cigarettes three times a day reduced HIV-SN pain by 34%, significantly more than the 17% reduction with placebo cigarettes. A >30% reduction in pain has been validated as a clinically significant level of improvement.[23] In the current study, half (52%) of those randomized to cannabis experienced at least a 30% reduction in pain, while a quarter (24%) of those randomized to placebo experienced a similar reduction in pain.

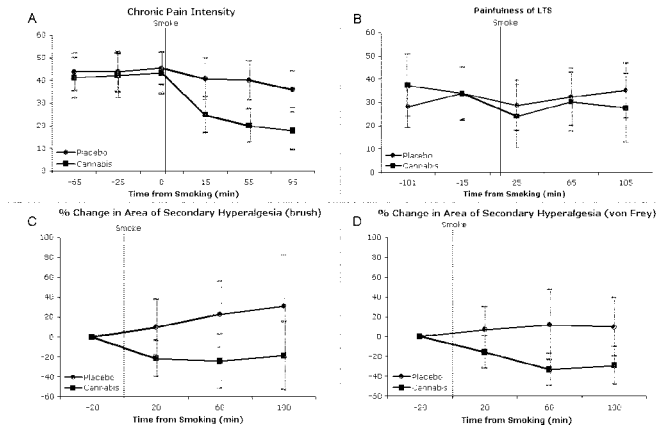

Figure 4. First smoking session: time course during the first 95 minutes after smoking of intensity of chronic pain as measured on the visual analog scale (A; cannabis n = 25, placebo n = 25), painfulness of LTS (B; cannabis n = 14, placebo n = 16), and areas of secondary hyperalgesia to brush and von Frey hair stimulation (C and D; cannabis n = 14, placebo n = 16). Mean ± 95% CI.

***Table 2** Mean side effect scores by study group*

	Adjusted estimates	
	Cannabis, mean (95% CI)	Placebo, mean (95% CI)
Anxiety*	0.25 (0.14, 0.44)	0.10 (0.05, 0.22)
Sedation†	0.54 (0.36, 0.81)	0.08 (0.04, 0.17)
Disorientation†	0.16 (0.07, 0.34)	0.01 (0.00, 0.04)
Paranoia	0.13 (0.03, 0.45)	0.04 (0.01, 0.14)
Confusion†	0.17 (0.07, 0.39)	0.01 (0.00, 0.06)
Dizziness†	0.15 (0.07, 0.31)	0.02 (0.01, 0.05)
Nausea	0.11 (0.04, 0.30)	0.03 (0.01, 0.14)

Side effects were rated three times daily on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

* p, 0.05; † $p < 0.001$.

In this randomized, placebo-controlled study, the number needed to treat (NNT) on the primary outcome measure of >30% pain reduction among all completing patients was 3.6 (1/[52%−24%]). Trials vary in their primary outcome measure, so comparing NNT figures only approximates relative potency. The NNT for lamotrigine was 5.4 for HIV-related painful DSP.[4,24] Although one group of investigators reported success with gabapentin, their data analysis does not allow calculation of an NNT.[5] The NNT in the present study is comparable to that reported in trials of gabapentin for other types of chronic neuropathic pain. In a large study of gabapentin for postherpetic neuralgia the NNT was 3.4 and for diabetic neuropathy the NNT was 4.0.[25,26] A recent meta-analysis of 107 controlled trials for neuropathic pain showed that only tricyclic antidepressants and higher potency opioids consistently achieved NNT values lower than 3.7.[24] However, for HIV-SN, tricyclic antidepressants were not effective.[9,10] Opioids have not been systematically evaluated for painful HIV-SN, but studies show efficacy across a broad spectrum of neuropathic pain disorders.[27,28]

In addition to patient-reported changes in ongoing chronic pain, smoked cannabis attenuated the cutaneous hyperalgesia associated with central neuronal sensitization produced by a standardized experimental pain model. Although one cannot entirely exclude pain relief due to relaxation, a high, or unblinding, the mood effects recorded argue against such an explanation. Only one of the six Profile of Mood States subscales (depression-dejection) showed a significant group difference, and actually favored placebo. Moreover, ratings of side effects in the cannabis group

were low. The rigorous experimental pain model outcome measures are novel to each patient and not strongly associated with expectations of relief of chronic pain. Areas of secondary hyperalgesia are mapped by an investigator while the patient looks away, and thus may be less subjective than pain intensity ratings on a VAS scale. Therefore, the present study provides evidence that cannabis has analgesic effects on acute central neuronal sensitization produced by the experimental pain model as well as on the neuronal mechanisms associated with painful HIV-SN.

The results reported here in neuropathic pain patients exposed to an experimental pain model are consistent with preclinical pain model studies with cannabinoids. Systemic cannabinoids are effective in animal models of acute mechanical and thermal pain, inflammation and hyperalgesia, and nerve injury.[29-35] In healthy human volunteers, smoked cannabis increased pressure pain tolerance thresholds.[36] The present study in chronic pain patients also shows an effect on experimental hyperalgesia. Although smoked cannabis did not appear to suppress the painfulness of the LTS procedure (analogous to the hot plate or tail flick test in animals), this may reflect the relatively low concentration of delta-9-THC in the study cigarettes.

The clinical literature on cannabinoids for pain conditions other than HIV-SN is limited and essentially restricted to isolated delta-9-THC preparations. Fifteen and 20 mg of delta-9-THC produced significant analgesia in cancer patients with pain, as well as antiemesis and appetite stimulation, but some patients reported unwanted side effects such as sedation and depersonalization at the 20 mg dose level.[37,38] In a follow-up study, 10 mg of delta-9-THC produced analgesic effects comparable to 60 mg of codeine, and 20 mg of delta-9-THC was equivalent to 120 mg of codeine. Two recent placebo-controlled studies of cannabinoids for central neuropathic pain associated with multiple sclerosis produced results similar to the present study. In a crossover trial of synthetic delta-9-THC up to 10 mg/day, an NNT of 3.5 was reported.[39] A trial of a sublingual spray containing delta-9-THC alone or combined with cannabidiol showed a 41% pain reduction with active drug vs a 22% reduction with placebo.[40]

The Institute of Medicine report on cannabis and medicine concluded that cannabinoids likely have a natural role in pain modulation, control of movement, and memory.[41] The Institute of Medicine report, along with other recent reviews, suggest that if cannabis compounds can be shown to have therapeutic value then the margin of safety is acceptable.[42,43] An acceptable safety margin has been shown in the present study as well as in a previous study of cannabinoids in patients with HIV-1 infection.[44]

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Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study

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Although cannabis may have potential therapeutic value, inhalation of a combustion product is an undesirable delivery system. The aim of the study was to investigate vaporization using the Volcano® device as an alternative means of delivery of inhaled *Cannabis sativa*. Eighteen healthy inpatient subjects enrolled to compare the delivery of cannabinoids by vaporization to marijuana smoked in a standard cigarette. One strength (1.7, 3.4, or 6.8% tetrahydrocannabinol (THC)) and delivery system was randomly assigned for each of the 6 study days. Plasma concentrations of Δ-9-THC, expired carbon monoxide (CO), physiologic and neuropsychologic effects were the main outcome measures. Peak plasma concentrations and 6-h area under the plasma concentration–time curve of THC were similar. CO levels were reduced with vaporization. No adverse events occurred. Vaporization of cannabis is a safe and effective mode of delivery of THC. Further trials of clinical effectiveness of cannabis could utilize vaporization as a smokeless delivery system.

The Institute of Medicine (10 m) report on Marijuana as Medicine published in 1999 concluded that "scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, appetite stimulation; smoked marijuana, however is a crude THC delivery system that also delivers harmful substances".[1] The report recommended that clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid onset, reliable, and safe delivery systems. While acknowledging therapeutic potential, the IOM report stressed that cannabis is not a completely benign substance, but a powerful drug with a variety of effects, but "except for the harms associated with smoking, the adverse effects are within the range of those tolerated for other medications." The report comments that "because of the health risks associated with smoking, smoked cannabis should generally not be recommended for long-term medical use. Nonetheless, for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern." The Institute of Medicine sends a clear message suggesting that smoking is not a desirable delivery system for the potential therapeutic effects of cannabis.

Cannabis vaporization is a technology for delivering inhaled tetrahydrocannabinol (THC) and other cannabinoids while reducing toxic byproducts of smoked cannabis primarily caused by combustion.[2,3] By heating cannabis to a temperature between 180 and 200°C, it is possible to vaporize the cannabinoids that reside on the trichomes on the surface of cannabis flowers and leaves, while avoiding combustion (which occurs at 230°C and above) and attendant smoke toxins. Vaporization is a relatively new technology. Various vaporizer designs are currently under development. The feasibility of vaporization of THC has been demonstrated in a series of laboratory studies involving different vaporizer designs.[2] An electric vaporizer was shown to release substantial amounts of the THC while producing no measurable amounts of the benzene, toluene, and naphthalene, which are generated when marijuana is smoked. Reductions in carbon monoxide (CO) and tar generation were also observed under vaporization compared to smoking. Although no measurements were made of other smoke toxins, it is quite possible that the vaporizer eliminated or substantially reduced the polycyclic aromatic hydrocarbons and other combustion-generated toxins commonly found in cannabis smoke, as they form at the higher temperatures of pyrolysis.

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A recent evaluation of the Volcano® vaporizer device used herbal cannabis or pure cannabinoid ethanolic solution preparations to test the efficacy and reproducibility of THC delivery into the balloon receptacle.[4] Cannabinoids were measured in the THC-containing materials before and after vaporization, and in the vapor that was generated by the device and collected within the balloon. The results validated the Volcano® vaporizer as an efficient and reproducible mode of delivery of Δ-9-THC. On average, 54% of the applied dose of THC was recovered in the balloon receptacle.

This study investigated vaporization using the Volcano® device compared to smoked cannabis. This is the first pharmacokinetic and pharmacodynamic evaluation conducted in humans to determine whether the Volcano® may be an appropriate system for use in clinical effectiveness studies.

RESULTS

Baseline characteristics of study subjects

A total of 68 patients were screened for eligibility between August 2004 and May 2005. Of these, 47 were not enrolled (33 patients were unavailable to commit to a 6-day hospitalization, 10 patients were excluded as a result of their medical history or concurrent illness, and four patients were excluded because of active substance abuse). Twenty-one patients were randomly assigned; however, three patients did not complete the intervention of the study phase (one patient for non-adherence to the General Clinical Research Center (GCRC) rules of comportment, one patient for acute influenza, and one patient withdrew consent), leaving 18 total patients for analysis.

Participants were predominately men (83%), Caucasian (72%), with some college education (94%). All of the participants were active marijuana users (median 5–6, range 3–10 marijuana cigarettes in the past 30 days). None had used the Volcano® device, although one participant had previously experienced vaporized marijuana using a similar device.

Primary outcome measure

The mean and 95% confidence intervals (CIs) for the plasma concentrations of THC at each time point for each strength of THC using both vaporization and smoking are presented in **Figure 1**. The vaporizer resulted in higher plasma concentrations of THC compared to smoked marijuana at 30 and 60 min at each strength (**Table 1**). The two modalities were not significantly different from one another at any of the three strengths in the 6-h area under the plasma THC concentration–time curve (AUC), or for the peak THC plasma concentrations measured at 2 min.

There was evidence of decreasing bioavailability and/or titration of THC intake with increasing strength of THC. The plasma THC AUC derived from the vaporizer normalized for the THC strength was highest at 1.7% THC (27.1 ng h/ml/%) and was progressively lower at higher THC strengths (3.4% THC: 20.5 ng h/ml/% and 6.8% THC: 14.3 ng h/ml/%; **Table 1**), suggesting higher bioavailability and/or more intensive puffing at lower THC potency. This decline was

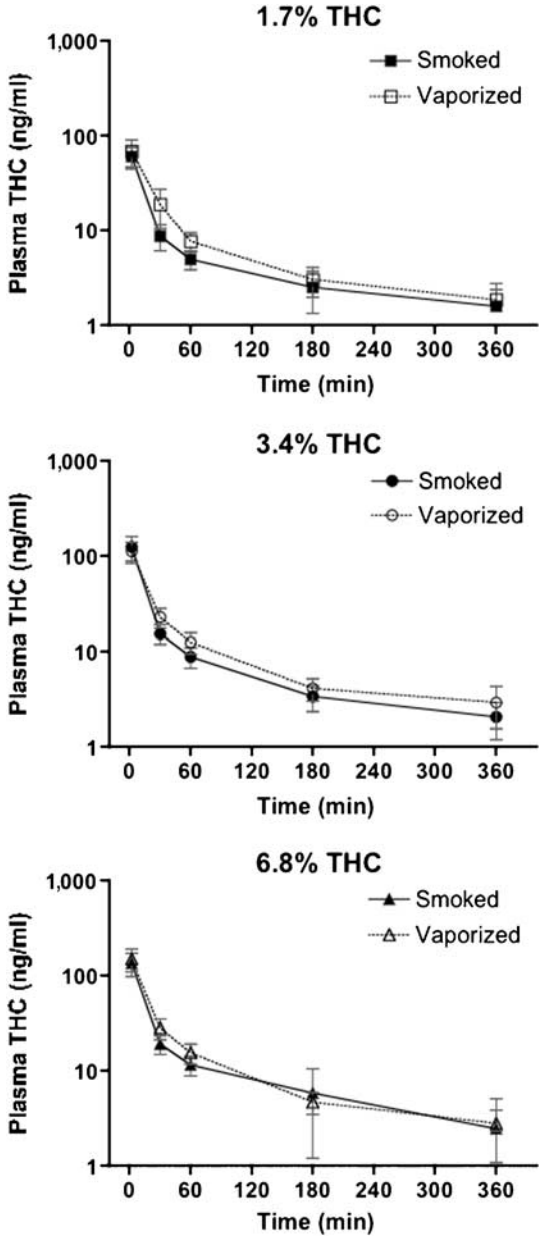

Figure 1 Plasma THC using vaporizer and smoked cannabis by THC strength (mean and 90% CI).

statistically significant (ratio: 0.87; 95% CI: 0.84, 0.90; $P<0.001$ per 1% increase in THC strength) and did not appear to differ between vaporization and smoking (ratio for interaction: 0.92; 95% CI: 0.79, 1.05; $P=0.25$) in a mixed model which included fixed effects for randomization, a linear term for THC strength, and a term for the interaction between these effects.

There was also evidence of titration of intake of THC with increasing THC strength based on puffing behavior. The number of puffs taken using smoked marijuana remained stable with increasing strength THC (mean puffs, 95% CI: 6.1 (4.8, 7.3), 5.9 (4.9, 6.8), and 6.4 (5.3, 7.6) for 1.7, 3.4, and 6.8% THC, respectively; mixed model analysis ratio: 1.01; 95% CI: 0.96, 1.05; $P=0.81$). The number of puffs taken

Table 1 THC pharmacokinetics for vaporized cannabis and ratio of vaporized vs smoked cannabis[a,b]

	Vaporizer				Vaporizer/smoked ratio		
THC, % outcome measure	Mean	95% CI	Minimum	Maximum	Odds ratio	95% CI*	*P*-value
1.7%							
AUC_{0-6}	46.00	34.89, 57.11	15.59	98.08	1.26	0.94, 1.68	0.12
C_{max} (=C_2)	68.95	46.99, 90.91	6.00	186.20	1.01	0.65, 1.58	0.97
C_{30}	18.94	10.57, 27.32	4.90	79.90	1.95	1.37, 2.80	0.001
C_{60}	7.56	6.02, 9.50	3.70	16.50	1.56	1.26, 1.93	0.001
C_{180}	3.05	1.99. 4.00	0.10	9.40	1.31	0.83, 2.06	0.25
C_{360}	1.87	0.97, 2.77	0.20	8.20	1.17	0.82, 1.66	0.38
Puffs	10.06	8.81, 11.30	7.00	17.00	1.71	1.47, 2.00	0.001
AUC/THC %	27.06	20.52, 33.60	9.17	57.69	1.26	0.94, 1.68	0.12
3.4%							
AUC_{0-6}	69.76	52.91, 86.62	22.30	140.44	0.99	0.81, 1.21	0.95
C_{max} (=C_2)	112.45	84.55, 140.65	36.70	201.10	1.07	0.64, 1.80	0.80
C_{30}	23.04	17.74, 28.35	28.35	43.20	1.50	1.29, 1.73	0.001
C_{60}	12.58	9.46, 15.70	3.30	24.20	1.41	1.11, 1.79	0.006
C_{180}	4.14	3.05, 5.24	1.40	10.10	1.24	1.06, 1.46	0.008
C_{360}	2.94	1.55, 4.34	0.60	12.90	1.34	1.03, 1.75	0.03
Puffs	9.17	8.23, 10.10	4.00	13.00	1.58	1.36, 1.84	0.001
AUC/THC %	20.52	15.56, 25.48	6.56	41.31	0.99	0.81, 1.21	0.95
6.8%							
AUC_{0-6}	96.79	67.51, 126.06	18.98	278.20	1.22	0.98, 1.54	0.08
C_{max} (=C_2)	187.12	100.65, 273.59	22.50	813.20	1.19	0.86, 1.65	0.30
C_{30}	28.80	22.19, 35.41	9.20	50.00	1.45	1.16, 1.82	0.001
C_{60}	15.99	12.41, 19.58	4.60	29.40	1.38	1.13, 1.69	0.002
C_{180}	4.81	3.65, 5.96	1.10	9.20	1.15	0.88, 1.52	0.31
C_{360}	2.99	0.79, 5.20	0	19.50	0.88	0.53, 1.45	0.62
Puffs	8.55	7.72, 9.40	5.00	11.00	1.43	1.11, 1.85	0.006
AUC/THC %	14.23	9.93, 18.54	2.79	40.91	1.22	0.98, 1.54	0.08

AUC, area under the curve; CI, confidence interval; THC, tetrahydrocannabinol. [a]AUCs in ng h/ml; C_{max} values in ng/ml. [b]Analysis conducted using mixed models to adjust for day of observation.

using vaporized marijuana tended to decrease with increasing strength of THC, but the trend was not significant (mean puffs, 95% CI: 10.1 (8.8, 11.3), 9.2 (8.2, 10.1), and 8.6 (7.7, 9.4) for 1.7, 3.4, and 6.8% THC, respectively; mixed model ratio: 0.97; 0.92, 1.01; $P = 0.17$).

Secondary outcome measures

The levels of exhaled CO increased very little after vaporization; mean = −1.9 p.p.m.; 95% CI: −4.4, 0.6 for 1.7% THC; mean = −1.8 p.p.m.; 95% CI: −3.7, 0.7 for 3.4% THC; and mean = −0.5 p.p.m.; 95% CI: −1.9, 0.9 for 6.8% THC), whereas there was a substantial increase after smoking marijuana (mean = 15.5 p.p.m.; 95% CI: 11.0, 20.1 for 1.7% THC; mean = 11.9 p.p.m.; 95% CI: 6.8, 17.1 for 3.4% THC; mean = 7.0 p.p.m.; 95% CI: 4.0, 10.0 for 6.8% THC) (**Figure 2**). This difference was statistically significant ($P < 0.001$) at each THC strength. The increase in CO (AUC for CO) decreased during smoking ($P = 0.003$ for trend), but not vaporization ($P = 0.25$) with increasing THC strength. The expired CO AUC per puff is an indicator of how much smoke is inhaled per puff for the smoked marijuana. The CO AUC per puff decreased progressively (1.7% THC: [mean, 95% CI]: 2.8 (2.2, 3.3); 3.4% THC: 2.1 (1.1, 3.0); 6.8% THC: 1.2 (0.6, 1.9); $P < 0.001$ for trend), consistent with taking smaller puffs with increasing THC content in the marijuana.

Subjective and safety observations

Self-reported high did not differ during vaporization compared to smoking overall (6-h AUC) or at any observation after consumption of cannabis (**Figure 3**). Self-reported high did increase significantly during both vaporization and smoking with increasing strength of THC ($P < 0.001$).

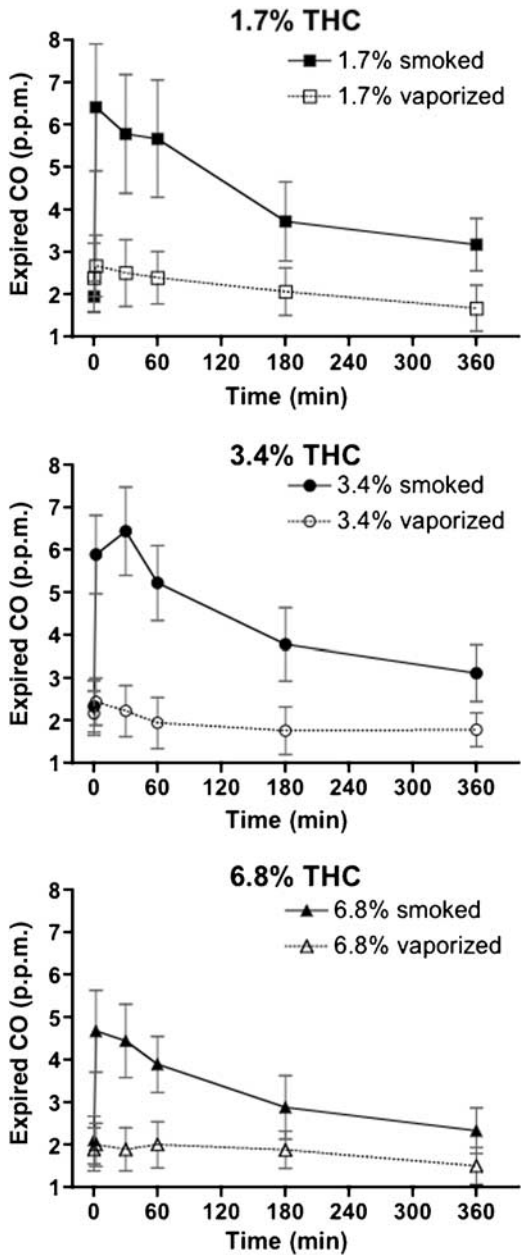

Figure 2 Expired CO at each time point for each mode of administration and THC strength (mean and 95% CI).

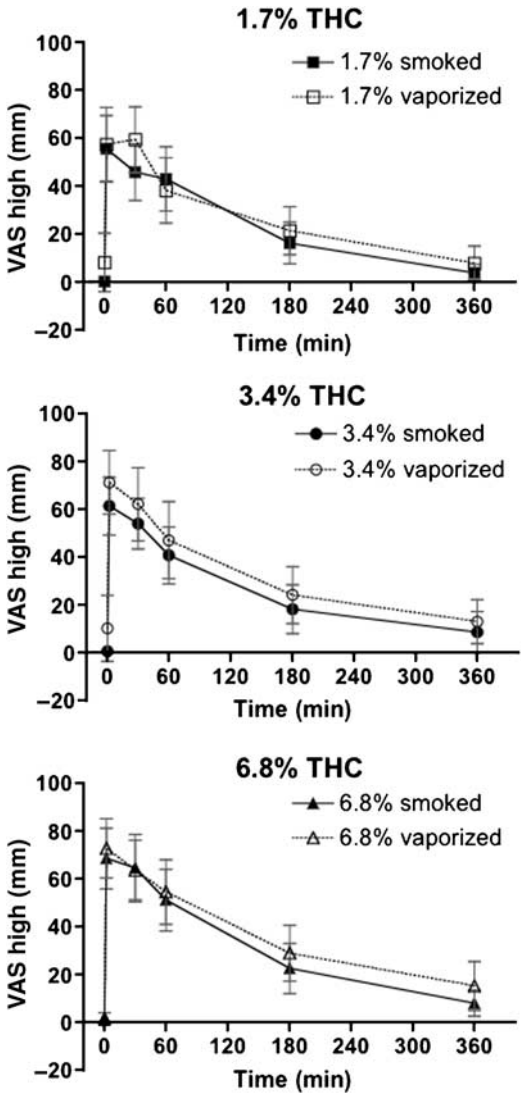

Figure 3 Self-reported "high" at each time point for each mode of administration and THC concentration (mean and 95% CI).

Although blinded with regard to dose, eight participants selected the day they received 3.4% THC (seven vaporized, one smoked) as their most preferred treatment day; four participants selected the day they received 6.8% THC via vaporization, and six participants had no treatment day preference. Overall, vaporization was the preferred method of administration by 14 participants, smoking was preferred by two, and two reported no preference. During the course of the study, no adverse events were reported.

DISCUSSION

Our study provides novel data on the absorption of THC from marijuana inhaled via the Volcano® vaporizer system compared to smoking marijuana cigarettes. We found that THC levels were generally similar over 6 h for the two types of delivery. The vaporizer was associated with higher plasma THC concentrations at 30 min and 1 h compared to smoking at each THC strength, suggesting that absorption was faster with the vaporizer.

Bioequivalence criteria developed for drugs require that the CIs for the ratios of AUC for the test and reference products be between 80 and 125% to be judged bioequivalent.[5] Using these criteria, we were not able to establish the bioequivalence of vaporization and smoking of marijuana. A much larger study would be needed to establish bioequivalence in this setting.

Of interest was that the systemic dose of THC, as estimated by the plasma AUC, normalized for the THC content of the cannabis, varied with THC strength. The dose of THC normalized for concentration of THC in the cannabis was greater at lower compared to higher THC strengths, both

for vaporized and smoked cannabis. This observation suggests either dose-dependant bioavailability or self-titration of THC intake. Self-titration of drug intake means that smokers adapt their smoking behavior to obtain desired levels of THC from the particular delivery system, taking more puffs and/or inhaling more efficiently at lower compared to higher THC strengths. Supporting the idea of titration was the trend to take more puffs at lower THC concentrations of vaporized marijuana and the higher CO per puff at lower THC concentrations of smoked marijuana. The phenomenon of self-titration of psychoactive drug intake from an inhaled delivery system is well documented for nicotine from cigarette smoking,[6] but to our knowledge has not been previously reported for marijuana.

Whereas smoking marijuana increased CO levels as expected for inhalation of a combustion product, there was little if any increase in CO after inhalation of THC from the vaporizer. This indicates little or no exposure to gaseous combustion toxins. Combustion products are harmful to health and reflect a major concern about the use of marijuana cigarettes for medical therapy as expressed by the Institute of Medicine. Although we did not measure other combustion products such as polycyclic aromatic hydrocarbons and oxidant gases, the observation of little or no CO exposure suggests little or no exposure to these other compounds. The vaporizer was well tolerated, with no reported adverse effects. Most subjects preferred the vaporizer compared to marijuana smoking, supporting its potential for medical therapy. Thus, the Volcano® is an acceptable system and may provide a safer way to deliver THC than smoking marijuana cigarettes.

In summary, we provide data indicating that the availability of THC delivered by the Volcano® vaporizer is comparable to that of marijuana cigarettes. Vaporization of marijuana does not result in exposure to combustion gases, and therefore is expected to be much safer than smoking marijuana cigarettes. The vaporizer was well tolerated and preferred by most subjects compared to marijuana cigarettes. The Volcano® device is an effective and apparently safe vehicle for THC delivery, and warrants further investigation in clinical trials of cannabis for medicinal purposes.

METHODS

Study patients. Participants were healthy adults between the ages of 21 and 45 years who were current cannabis users and had smoked cannabis within the past 30 days but in an amount totaling less than 10 cannabis cigarettes or the equivalent. Subjects with active substance abuse (*e.g.*, recurrent or continuous drug and/or alcohol use) or diagnosed with marijuana dependence as defined in DSM-IV code no. 304.30. were excluded. Subjects were required to abstain from smoking cannabis for 48 h before their admission into the GCRC at San Francisco General Hospital (SFGH). The study was approved by the Institutional Review Board at the University of California San Francisco, the Research Advisory Panel of California, the Drug Enforcement Administration, the Food and Drug Administration, and the National Institute on Drug Abuse. Written informed consent was obtained from all patients. The trial was monitored by an independent Data Safety Monitoring Board (DSMB) established by the University of California Center for Medicinal Cannabis Research.

Study medication. The National Institute on Drug Abuse provided pre-rolled cannabis cigarettes, weighing on average 0.9 g and containing 1.7, 3.4, and 6.8% Δ-9-THC, respectively. The cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the San Francisco General Hospital General Clinical Research Center where the in-patient study was conducted. The cigarettes were bisected; one half to be smoked and the contents of the other half to be vaporized. The half cigarettes were rehydrated in a humidifier overnight before their use. Patients were housed in a room with a fan ventilating to the outside. Research staff monitored patients during smoking sessions, weighed the cannabis cigarettes immediately before and after they were administered to patients, and returned all leftover material to the pharmacy. To maximize standardization of inhaled doses, patients followed the Foltin uniform puff procedure where inhalation for 5 s is followed by a 10 s breath hold, then exhalation; the entire process is repeated after 45 s.[7] Study participants smoked or vaporized cannabis once a day. Subjects were instructed to continue puffing until they exhausted smoke or vapor from the delivery device or until they had inhaled as much as they could tolerate.

The vaporizer device. The Volcano® vaporizer was obtained from Storz & Bickel GmbH & Company (Tuttlingen, Germany) and was employed according to the manual provided. The device works as a vaporizer that evaporates the active substances or aromas from plant material by using a hot airflow (**Figure 4**). Cannabis placed in the filling chamber is heated by the device to 190°C. The vaporized compounds are collected in the inflatable, detachable bag fitted with a mouthpiece and a one-way valve that allows the vapor to remain in the balloon until inhalation. It required two to three balloon inflations to vaporize each half cigarette. Subjects also followed the Foltin puff procedure when inhaling the vaporization product.

Study design and procedures. The study was a 6-day "proof of concept" pilot study to investigate the delivery of cannabinoids by way of vaporization of cannabis compared to cannabis smoked in a standard cigarette. The in-patient setting permitted us to measure plasma THC concentration over time and to rigorously assess the primary and secondary outcome variables in a controlled clinical environment.

Screening visit. Once a subject for the protocol had been identified, details of the study were carefully discussed and the subject was asked to read and sign a consent form. Subjects were asked questions about their medical history including psychiatric illness and substance abuse. Subjects were asked to abstain from smoking or ingesting cannabis 48 h before their hospitalization based on our prior studies which indicated that after 24 h of abstinence, plasma THC concentrations are sufficiently low so that the concentration-time curve could be determined after the experimental exposure.[8]

GCRC in-patient hospitalization (days 1-6). Subjects inhaled three strengths of cannabis (1.7, 3.4, and 6.8% THC) as smoked cigarettes and three as vaporized cannabis using the Volcano® device. Half of one cigarette was inhaled via one of the two delivery systems on each of the 6 in-patient GCRC days. The uniform puff procedure described above was utilized to attempt to standardize inhalation. Blood was drawn at 2, 30, 60, 180, and 360 min after smoking on each of the 6 inhalation days to measure the concentrations of THC. Expired CO was measured using the Ecolyzer® before inhalation, and 2, 30, 60, 180, and 360 min after inhalation.

Subjects rated the subjective "high" they experienced using a 100 mm visual analog scale anchored by "none" and "highest ever". On day 5 before discharge, subjects were asked to choose which in-patient day they preferred. Subjects were asked to rate their preferences from 1 to 5 with 1 indicating very satisfied and 5 indicating very dissatisfied.

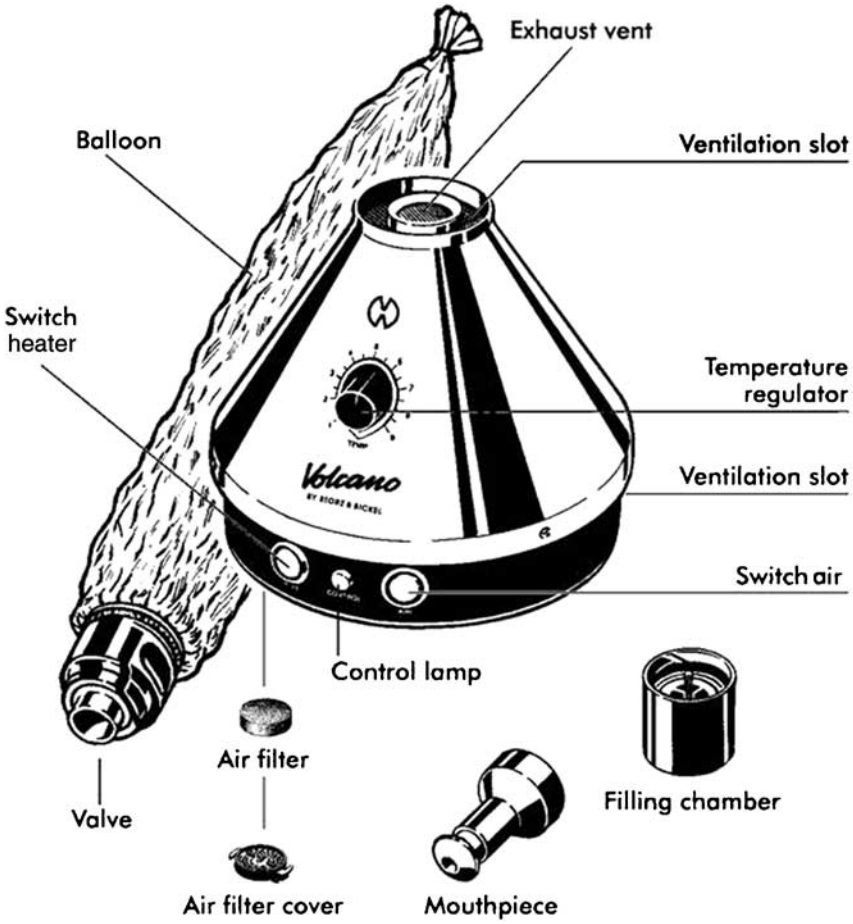

Figure 4 Volcano® apparatus.

All adverse events were spontaneously reported by the subject or observed by the study personnel and/or GCRC nursing staff, documented along with any medical intervention, and evaluated according to standardized criteria in terms of severity, frequency, duration, and relationship to study drug. Adverse events were graded using the NIH Division of AIDS table for scoring severity of adult adverse experiences.[9]

Randomization. The order of administration of the six combinations of THC strength and delivery method for the 18 participants was randomized in three 6×6 Latin squares. This ensured balance in the sense that each of the six combinations occurred exactly three times on day 1, exactly three times on day 2, and so on. In addition, the orders were restricted so that the two delivery methods for the same strength always occurred on consecutive days. This was to prevent patients from developing an early preference for one delivery method if it was used with a higher strength cigarette than the other. Randomization was computer-generated, and study drug distribution was managed by a research pharmacist. Subjects and study personnel were blinded to the THC strength.

Statistical analysis. The 18-patient target sample size was based on a standardized effect size to calculate sample size and power for the study. With a sample of 18 subjects, we had an 80% power to detect a true standardized effect size (E/S) of 0.70, using an α of 0.05, where E is the effect size and S is the standard deviation of the paired differences.[10,11] This calculation assumes use of a paired t-test using data at a single concentration of THC.

The primary outcome was the within-person ratio for the 6-h area under the curve (AUC_{0-6}) for plasma concentration of THC, comparing the vaporizer with smoking cannabis cigarettes. AUC_{0-6} was computed using the linear trapezoidal method, assuming zero THC concentration at baseline. This assumption was based on our previous research that observed undetectable plasma concentration of THC 8 h after smoking in all subjects.[8] For each mode of administration and THC strength, we plotted the mean and 95% CIs of the observed values at each time point. To assess the within-person ratio comparing vaporization to smoking, each outcome (AUC_{0-6}, C_2, C_{30}, C_{60}, C_{180}, C_{360}, number of puffs, AUC_{0-6} per THC percent, and AUC_{0-6} per puff) was log transformed for analysis using mixed effects models. The overall effect of vaporization compared to smoking for each parameter was assessed by fitting a fixed effect term for randomization (vaporization vs smoking), controlling for strength of THC (indicators for 3.4% THC and 6.8% THC cannabis, relative to 1.7% THC cannabis). Each patient was treated as a random effect. Another model was fit to assess THC strength-specific effects of vaporization compared to smoking. This model included fitting additional fixed effects for the use of the vaporizer at each strength of THC (vaporization at 1.7% THC, vaporization at 3.4% THC, and vaporization at 6.8% THC).

We also assessed the potential presence of order effects due to the study day of observation, as well as potential practice effects due to additional experience using the vaporizer. To assess the presence of order effects, additional variables were added to both the overall and strength-specific models to assess whether day of observation impacted the outcomes, as well as whether there was a difference

in measurements taken on the first day of the study compared to other study days. In these models, day of observation was treated as a linear variable with and without an additional indicator variable for the first study day. Similarly, to assess the presence of practice effects, additional variables were added to both the overall and strength-specific models to assess whether previous use of the vaporizer impacted the outcomes. These models included either a linear variable for how many days the participant had used the vaporizer or separate indicator variables for each day of vaporizer use.

To explore possible evidence of titration of THC intake and dose-dependent changes in bioavailability, we created additional mixed models for number of puffs and AUC_{0-6} per THC percent, which included fixed effects, as above, for randomization (vaporization vs smoking), as well as linear terms for strength of THC, and the interaction between randomization and strength of THC. As above, these models included a random effect for each patient. These models assess not only whether the ratio of the number of puffs or the AUC per THC percent differs during vaporization and smoking but also whether the ratio increases or decreases with increasing strength of cannabis, and whether this increase or decrease differs during vaporization compared to smoking.

We compared the observed values for expired CO and self-reported high using similar methods. We plotted the mean and 95% CIs of response measures at each time point for each mode of administration and THC strength. We also fit mixed models for the 6-h AUC for expired CO and self-reported high, as described above, to compare within-person effects using vaporization and smoking. For 6-h AUC for CO, we fit models for the within-person arithmetic difference in effects, because we were unable to fit models for the ratio of effects for 6-h AUC for CO due to the presence of many negative values (and therefore non-valid log transformation of these values) during vaporization. For 6-h AUC for self-reported high, we fit models for the within-person ratios in effects, as above.

All analyses were conducted using SAS 8.2.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Short-Term Effects of Cannabinoids on Immune Phenotype and Function in HIV-1-Infected Patients

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Cannabinoids, including smoked marijuana and Δ^9-tetrahydrocannabinol (THC) (dronabinol, Marinol), have been used to treat human immunodeficiency virus-1 (HIV)–associated anorexia and weight loss. Concerns have been raised, however, that these compounds might have adverse effects on the immune system of subjects with HIV infection. To determine whether such effects occur, the authors designed a randomized, prospective, controlled trial comparing the use of marijuana cigarettes (3.95% THC), dronabinol (2.5 mg), and oral placebo in HIV-infected adults taking protease inhibitor-containing highly active antiretroviral therapy (HAART). Assays of immune phenotype (including flow cytometric quantitation of T cell subpopulations, B cells, and natural killer [NK] cells) and immune function (including assays for induced cytokine production, NK cell function, and lymphoproliferation) were performed at baseline and weekly thereafter. On the basis of these measurements and during this short 21-day study period, few statistically significant effects were noted on immune system phenotypes or functions in this patient population.

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In the era prior to the introduction of highly active antiretroviral therapy (HAART), and largely in the absence of any supporting data, smoked marijuana became increasingly used for the treatment of human immunodeficiency virus-1 (HIV)–associated anorexia and weight loss.[1] Legislation was passed in California in 1996 that enabled physicians to recommend marijuana for a number of medical conditions, including the AIDS wasting syndrome. Access to smoked marijuana was facilitated in the San Francisco Bay Area by the creation of numerous cannabis "buyers clubs."[2] At one time, it was estimated that such establishments were providing marijuana to more than 10,000 clients with HIV infection.

Despite anecdotal reports of weight gain and improvement in mood and quality of life in their patients who smoked marijuana, medical providers caring for patients with HIV infection have raised concerns about the safety of marijuana smoking by patients with immune deficiency. Studies of the effect of marijuana on immunity have been contradictory and, when viewed in aggregate, difficult to interpret. The major psychoactive component of marijuana, Δ^9-tetrahydrocannabinol (THC), has been reported to suppress immune functions such as cell proliferation, antibody production, natural killer (NK) cell activity, and macrophage function; to dysregulate production of proinflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α); and to confer altered susceptibility in vivo to infection with intracellular organisms such as *Legionella pneumophilia* and to herpes simplex virus type-1 infected cells.[3-10]

Two cannabinoid receptors, CB1 and CB2, have been identified.[11] The CB1 receptor, which is preferentially expressed in the brain, has been identified as the

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likely cause of cannabis-mediated central nervous system effects. In contrast, the CB2 receptor is preferentially expressed in peripheral tissues such as the marginal zone of the spleen and on the surface of B lymphocytes and NK cells.[12] Accordingly, the potential exists for interactions between THC and the immune system.

To date, there have been no controlled investigations of the impact of marijuana on immune function in patients with HIV infection. Either as a stimulant or suppressant of immune function, marijuana could potentially lead to increased viral burden. This potential effect also has never been investigated in a prospective, controlled fashion. Finally, the potential for a drug-drug interaction between protease inhibitors and marijuana is particularly worrisome because both are metabolized by the cytochrome P450 enzyme system, and many HIV-infected patients continue to smoke marijuana as an appetite stimulant or to decrease nausea associated with their antiretroviral therapy.[13-16]

To more closely evaluate the possibility of these adverse effects, we designed a study to determine the safety/toxicity profile of cannabinoids in people with HIV infection on protease inhibitor-containing regimens. The specific goals of this study were to determine the short-term effects of cannabinoids (smoked and oral) on HIV RNA levels, the immune system, and the pharmacokinetics of two widely used protease inhibitors, indinavir and nelfinavir. Viral load was selected as the primary endpoint because it might be affected by an interaction between cannabinoids and the metabolism of the protease inhibitor and/or between cannabinoids and the immune system. Reported here are the immune endpoints of this study of the short-term effects of cannabinoids in patients with HIV infection. Published data are reported separately on the short-term effects of cannabinoids on viral load and on the pharmacokinetics of the protease inhibitors.[17,18]

METHODS

Study Population

Subjects were required to be at least 18 years old, have documented HIV infection, and be on a stable antiretroviral treatment regimen that included either indinavir (Crixivan, Merck) or nelfinavir (Viracept, Agouron) for at least 8 weeks prior to enrollment. Upon admission to the San Francisco General Hospital General Clinical Research Center (GCRC) for the 25-day inpatient trial, subjects who had been taking the more recently recommended dose of nelfinavir (1250 mg twice daily) were switched to a dose of 750 mg three times daily for consistency of our pharmacokinetic evaluations.[19] No additional protease inhibitors were allowed during the duration of the study. Subjects were also required to have a stable viral load, defined as less than a threefold ($< 0.5 \log_{10}$) change in HIV RNA level for the 16 weeks prior to enrollment. All subjects were required to have prior experience smoking marijuana (defined as six or more times) to ensure that they knew how to inhale and what neuropsychiatric effects to expect. The study was approved by the Committee on Human Research of the University of California, San Francisco, and signed informed consent was obtained from each participant before enrollment.

Exclusion criteria included the following: any active opportunistic infection or malignancy requiring acute treatment, unintentional loss of ≥ 10% of body weight during the prior 6 months, current substance dependence, methadone maintenance, use of tobacco or cannabinoids (smoked or oral) within 30 days of enrollment, history of serious pulmonary disease, pregnancy, and Stage II or higher AIDS dementia complex. Laboratory exclusion criteria were as follows: hematocrit < 25% and hepatic transaminase elevations greater than five times the upper limit of normal. Therapeutic exclusions were concurrent use of megestrol acetate, nandrolone, oxandrolone, oxymetholone, human growth hormone, thalidomide, pentoxifylline, prednisone, interleukin-2, chemotherapy, radiotherapy, or other investigational agents known to alter immune system function within the prior 8 weeks.

Study Medications

The National Institute on Drug Abuse (NIDA) provided prerolled marijuana cigarettes, weighing on average 0.9 gm and containing 3.95% THC. These cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the GCRC where the inpatient study was conducted. The marijuana cigarettes required rehydration overnight in a humidifier. Subjects randomized to the smoked marijuana arm were housed in a room with a fan ventilating to the outside. To maximize standardization of inhaled doses, research staff monitored subjects while they followed the Foltin uniform puff procedure.[20] Research staff weighed the marijuana cigarettes immediately before and after they were administered to subjects and returned all leftover material to the pharmacy for ultimate return to NIDA. Subjects smoked up to three com-

plete marijuana cigarettes daily, as tolerated, 1 hour prior to meals. Roxane Laboratories (Columbus, OH) supplied dronabinol and matching placebo capsules.

Research Design and Procedures

Subjects were randomized in a double-blind manner to the oral regimens and received either dronabinol 2.5 mg or placebo on the same schedule as the subjects randomized to smoked marijuana. The randomized, placebo-controlled trial was composed of two inpatient phases. The first phase was a 4-day lead-in period, during which time subjects were admitted to the GCRC for measurement of baseline parameters. A urine sample obtained on the day of admission (day –4) was required to be negative for THC. The second phase was a 21-day intervention period beginning with random assignment of treatments on day 0. The subjects were stratified by protease inhibitor (indinavir or nelfinavir) and then allocated with equal probability in blocks of 12 to the study agents (marijuana, dronabinol, and placebo). Subjects were not permitted to have visitors or to leave the confines of the GCRC unless accompanied by research personnel during the 25-day study. All clinical laboratory tests and study procedures were obtained or performed in the GCRC.

Absolute Lymphocyte Counts

Automated complete blood counts with differential were performed in the San Francisco General Hospital Clinical Laboratory, using an automated hematology analyzer (Bayer Technicon H3 System, Bayer Corp., Tarrytown, NY) according to the manufacturer's directions.

Immunophenotyping

Baseline samples were collected on day 0, and follow-up specimens were drawn on days 7, 14, and 21. Four-color flow cytometric immunophenotyping was performed according to the manufacturer's directions with the following panels of antibodies: CD3-Cy5/CD4-PE/CD8-ECD/CD45-FITC, CD3-ECD/CD19-FITC/CD56-PE/CD45-Cy5, CD4-ECD/CD8-Cy5/CD38-PE/HLA-DR-FITC, CD4-ECD/CD8-Cy5/CD25-FITC/CD69-PE, CD4-ECD/CD8-Cy5/CD45RA-FITC/CD62L-PE (all from Beckman Coulter, Inc., Fullerton, CA). Data acquisition and analysis were performed using a Beckman Coulter EPICS XL flow cytometer, running System II, version 3.0.

Cytokine Flow Cytometry

A cytokine flow cytometry assay was used to measure the percentage of CD4+ T cells that are activated (express CD69) and that also synthesize specific cytokines (TNF-α, IFN-γ, or IL-2) in response to stimulation with the CMV antigen.[21] As a positive control, stimulation was carried out with the superantigen *Staphylococcal* enterotoxin B (SEB), and unstimulated cultures served as negative controls. Briefly, heparinized blood was incubated with antibody to CD28 (L293, BD Biosystems, San Jose, CA) alone (negative control), with SEB (Sigma, St. Louis, MO), or with sucrose density gradient-purified virus preparations from human CMV strain AD169-infected human foreskin fibroblast cultures (Advanced Biotechnologies, Inc., Columbia, MD) for 5 hours. Brefeldin A (Sigma) was added during the last 3 hours, followed by addition of FACS™ lysing solution (BD Biosystems), centrifugation, and resuspension of cells in FACS™ permeabilizing solution (BD Biosystems). Cells were then stained with monoclonal antibodies specific for CD4, CD69, and either TNF-α, IFN-γ, or IL-2 and analyzed by flow cytometry. The frequency of CD4+ T cells staining positive for CD69 and for the intracellular cytokine of interest after CMV stimulation was adjusted by subtracting the frequency in unstimulated samples. In preliminary experiments, control stimulants included a mock-infected cell lysate–negative control preparation (BioWhittaker), tissue culture medium including 10% human AB serum, and no stimulation. No significant difference was noted among these negative controls.

Natural Killer Cell Function

The cytolytic activity of NK cells was assessed using K562 erythroleukemic target cells.[22] K562 cell suspensions were labeled with ^{51}Cr for 2 hours at 37°C and supplemented with RPMI 1640 and 10% human AB serum. After centrifugation, cells were stained with trypan blue and counted. Peripheral blood mononuclear cells (PBMC) were isolated by density-gradient centrifugation, counted, adjusted to 1×10^7cells/ml, and plated in K562 cells at effector:target (E:T) ratios of 6.3:1, 12.5:1, 25:1, 50:1, and 100:1. Culture plates were centrifuged and incubated at 37°C with 5% CO_2 for 4 hours before being harvested and counted. Both net NK cell

cytotoxicity and per NK cell cytotoxicity were measured and expressed as percent lysis of target cells at each E:T ratio.

Lymphoproliferation

Lymphoproliferation was measured using a standard tritiated thymidine uptake assay.[23] Briefly, PBMC were incubated in quadruplicate with phytohemagglutinin (PHA, Sigma), tetanus toxin (Connaught Laboratories, Swiftwater, PA), CMV antigen (BioWhittaker), or a pool of inactivated alloreactive human PBMC for 3 to 6 days and then pulsed with 1 μCi of tritiated thymidine. Counts per minute (cpm) for each antigen were averaged and the stimulation index (SI) calculated. At least one HIV-uninfected control was run weekly throughout the course of the study. In all cases in which donor cell responses were found to be negative, positive responses were detected either for that donor with another antigen or for other donors assayed on the same day.

Statistical Analysis

The effects of cannabinoids on absolute lymphocyte counts, immunophenotyping analyses, and immune responses as measured by cytokine flow cytometry, NK cell assay, and lymphoproliferation assay were analyzed by comparison of the baseline (day 0) parameters with those derived after cannabinoid treatment (day 21). Median values of these variables for each arm at baseline are reported, as are median values for each arm based on the change in each variable between day 0 and day 21. Because many of the baseline and change variables were not normally distributed, nonparametric statistical tests were performed. Kruskal-Wallis tests were used to identify statistically significant differences between the placebo arm and each of the cannabinoid arms at baseline. Kruskal-Wallis tests were also used to identify statistically significant differences between the placebo arm and each of the cannabinoid arms based on the change in each variable between day 0 and day 21.

RESULTS

Subject Characteristics

Sixty-two patients completed the study. Twenty patients were randomized to smoke marijuana, 22 to take dronabinol, and 20 to take placebo. Of the patients, 55 were male, 3 were female, and 4 were male-to-female transgendered. Half (n = 31) of the patients were white, 12 were African American, 10 were Latino, and 9 were of mixed or other ethnicity. More than half of the patients (n = 33) were between the ages of 40 and 49, 18 were younger than 40, and 11 were age 50 or older.

Absolute Lymphocytes and Immunophenotyping

Figure 1 shows absolute lymphocyte counts and immunophenotyping results for percent CD4+ T cells, percent CD8+ T cells, percent naive CD4+ T cells, percent naive CD8+ T cells, percent memory/effector CD4+ T cells, percent memory/effector CD8+ T cells, percent CD3-CD19+ B cells, and percent CD3-CD56+ NK cells for all three arms over the 21 days of the study. There were no statistically significant differences in baseline values across the three arms for any of these variables. When we looked at change in these variables between day 0 and day 21, we found only one statistically significant difference when we compared patients in the cannabinoid arms with those in the placebo arm. Changes in absolute lymphocyte counts among those in the marijuana arm were significantly greater compared with changes in the placebo arm (median change = 300 vs. 0.00 cells/μl; p = 0.01).

Baseline values were significantly higher in the dronabinol arm compared with the placebo arm for four other immunophenotyping variables: %CD4+HLA-DR+ cells (median = 11.8 vs. 4.5; p = 0.03), %CD4+CD38+HLA-DR+ cells (median = 9.0 vs. 4.5; p = 0.04), %CD8+HLA-DR+ cells (median = 20.0 vs. 9.6; p = 0.01), and %CD8+CD38+HLA-DR+ cells (median = 13.2 vs. 5.2; p = 0.01). Although baseline values were also higher for each of these variables in the marijuana arm compared with the placebo arm, this difference was statistically significant only for %CD8+HLA-DR+ cells (median = 13.0 vs. 9.3; p = 0.03).

When we looked at change between day 0 and day 21, we observed significant negative changes in the dronabinol arm compared to the placebo arm for two variables: %CD8+CD38+HLA-DR+ cells (median change = –3.50 vs. 0.05; p = 0.001) and %CD8+CD69+ cells (median change = –0.30 vs. 0.05; p = 0.04). An additional negative change, which approached statistical significance, was seen in %CD4+CD38+HLA-DR+ cells (median change = –1.20 vs. –0.25; p = 0.06). However, two of these three variables, %CD8+CD38+HLA-DR+ and %CD4+CD38+HLA-DR+, were significantly higher in the dronabinol arm compared with the placebo arm at day 0. Therefore, the potential confounding

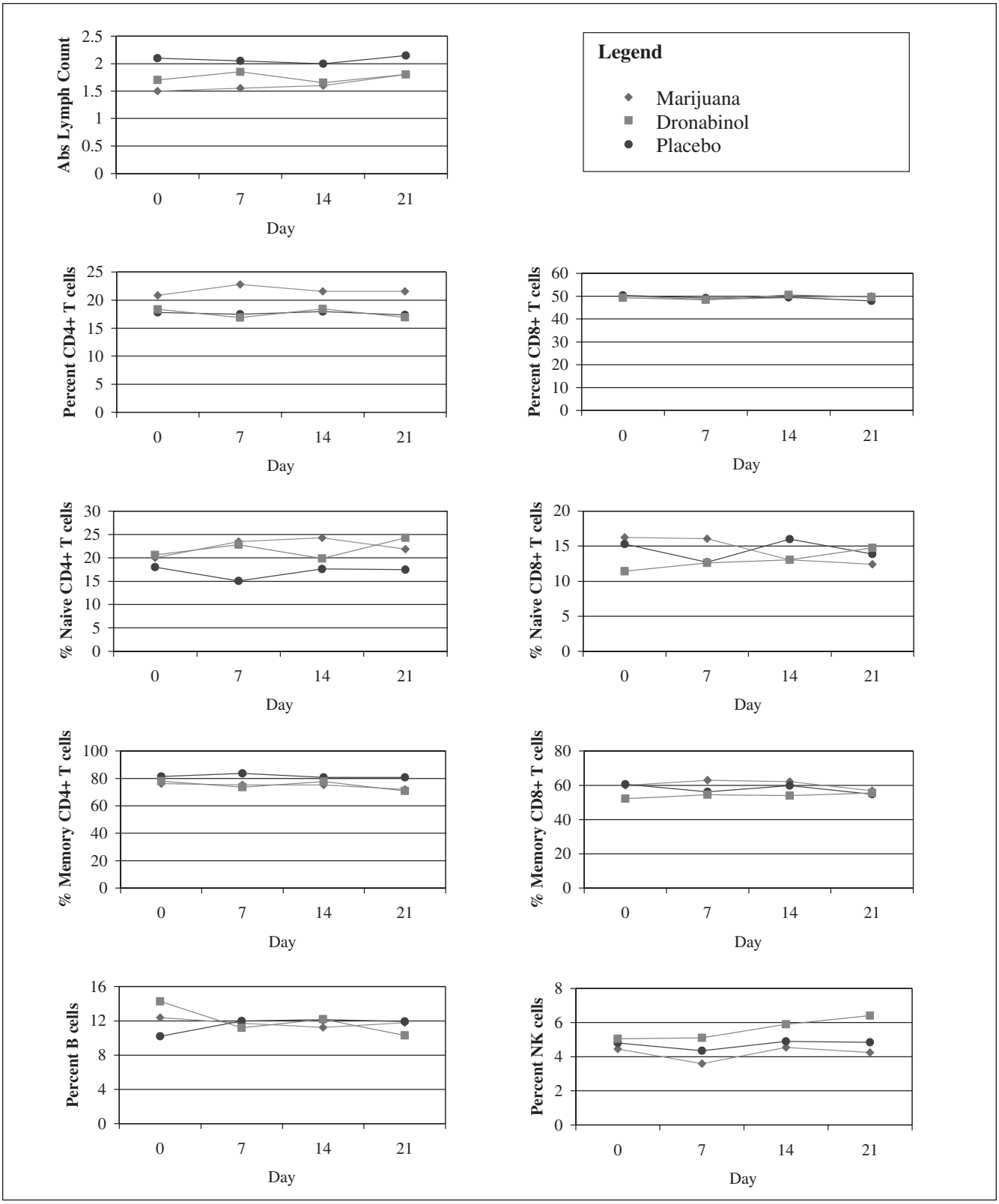

Figure 1. Median absolute and percent lymphocytes for selected variables by arm.

effect of these baseline differences on the subsequent apparent differences in change between day 0 and day 21 cannot be discounted.

When we compared values in the marijuana arm with those in the placebo arm for the other immunophenotyping variables, we did not observe any differences at baseline or in change between day 0 and day 21 that approached or achieved statistical significance.

Cytokine Flow Cytometry

No statistically significant differences were found between values in the placebo arm compared with the cannabinoid arms at baseline or in changes between day 0 and day 21 in each of the three groups. However, almost exclusively positive median changes were found in cytokine flow cytometry variables in each of the cannabinoid arms. Only one small negative median change in the dronabinol (CVM-stimulated CD69+/IL-2+ cells) and marijuana arms (CVM-stimulated CD69+/TNF-α cells) was seen.

Natural Killer Cell Function

No statistically significant differences were found in the activity of NK cells derived from patients on placebo and those on the cannabinoid arms on day 0. When patients on dronabinol were compared with those on placebo, no statistically significant differences were found in the change of NK activity from day 0 to day 21, although some interesting patterns could be observed. There was net negative NK cell activity among patients on dronabinol compared with those on placebo at all E:T ratios, except those with ratios of 12.5:1 and 6.3:1 (0.7 vs. –0.7 and –0.7 vs. –1.4, respectively). In contrast, there was a net positive median change in NK cell activity among patients on marijuana compared with those on placebo at all E:T ratios, except average spontaneous release (–4 vs. 274) and average maximum release (–1619 vs. 2354). These median differences were statistically significant for percent lysis using effector-to-target ratios of 50:1 (15.5 vs. 1.8; $p = 0.003$), 25:1 (6.4 vs. –0.9; $p = 0.01$), 12.5:1 (4.6 vs. –0.7; $p = 0.02$), and 6.3:1 (3.0 vs. –0.7; $p = 0.05$).

Lymphoproliferation Assay

Using stimulation with PHA, tetanus toxin, CMV antigen, and inactivated alloreactive human PBMC, no statistically significant differences and no predominant patterns between values in the placebo arm compared with the cannabinoid arms at baseline or in change between day 0 and day 21 were found. Only one value for median change in SI using 100,000 allo cells/well approached statistical significance (–4.4 vs. 6.4; $p = 0.08$), comparing patients on dronabinol with those on placebo.

DISCUSSION

Although cannabinoids are thought to exert a positive clinical benefit in some patients with HIV disease and wasting, concerns have been raised about their potential adverse effects on the immune system. Here, in the context of a randomized, prospective, placebo-controlled study comparing the short-term effects of cannabinoids in patients with HIV infection on a stable antiretroviral regimen, no such adverse effects have been observed. Specifically, patients randomized to smoked marijuana or dronabinol showed no clear discernible negative changes compared with placebo recipients, over the 21-day study period, in the percentage of circulating CD4+ and CD8+ T cells; in the representation of phenotypically described "naive" or "activated" T cell subpopulations; in immune responses to SEB and CMV, as measured by cytokine flow cytometry; in NK cell number and function; and in proliferation status in vitro in response to PHA, tetanus toxin, CMV, or alloantigen. The few changes that were noted, both positive and negative, though statistically significant, do not constitute any meaningful pattern of changes in immune phenotype or function. These results, coupled with concomitant studies showing no cannabinoid-associated effect on viral load[17] or on the metabolism of protease inhibitors,[18] indicate that this short-term use of cannabinoids is well tolerated in this patient population.

It has been hypothesized that previously described immune effects of marijuana may be related to THC-induced shifts in the balance of "Th1" and "Th2" cells.[24] In contrast, and as reviewed by Hollister,[25] many of the effects documented for THC have been observed in conditions, both in vivo and in vitro, in which supraphysiologic doses of the compound are used, controls with similar lipophilic properties are omitted, or both. Even relatively simple observations (e.g., that phytohemagglutinin and mixed-cell culture responses are suppressed in young, chronic marijuana smokers) have been difficult to reproduce.[26-28] More recently, conflicting reports have been generated regarding the impact of THC on levels of TNF-α. Whereas some investigators report THC inhibition of TNF-α,[7] another study using ELISA (enzyme-linked immunoabsorbant

assay) techniques demonstrated decreased interleukin-6 but increased TNF-α levels in a mouse macrophage system.[29]

Many of the reported studies of the immune effects of cannabinoids have been conducted in cell culture systems or animal models. Human studies have evaluated immune function in chronic marijuana smokers. To date, there have been no prospective clinical trials investigating the immune effects of smoked marijuana in patients with HIV infection. Retrospective analyses from the Multicenter AIDS Cohort Study evaluating outcomes in 1662 seropositive users of psychoactive drugs found that none of the drugs used by participants was associated with enhanced clinical or immunologic expression of HIV infection.[30] Of note, use of marijuana in the preceding 2 years was reported by 89% of the seropositive men in the cohort. This was consistent with findings from a previous observation from the San Francisco General Hospital experience.[31] A study of intravenous drug users with HIV infection determined that smoking of drugs such as marijuana was associated with an increased risk of bacterial pneumonia, although there were other confounding associations.[32]

In sum, this study revealed no evidence of detrimental effects of cannabinoids on any of the immune parameters measured. Our conclusions are limited by the short (21-day) duration of this study. In addition, the lack of a blinded control group for the smoked marijuana arm could lead to bias in interpreting some of the results of the main study (e.g., weight changes). However, it is difficult to attribute HIV-1 RNA and lymphocyte subset effects to any such potential bias. We chose not to include a smoked placebo group because we thought it would be impossible to blind marijuana in subjects with prior experience. The disparate results on the effects of THC on the immune system from prior studies may be related to differences in study populations, drug composition, drug concentration, or assay conditions. A key question now will be whether marijuana exerts significant immune effects when administered over longer periods of time.

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Cannabinoid–Opioid Interaction in Chronic Pain

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Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2–4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5. The extent of chronic pain was also assessed daily. Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration–time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis. We therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

Selecting an appropriate treatment for chronic pain remains problematic. Although opioids are effective analgesics, dose-limiting side effects such as sedation, nausea and vomiting, and fear of dependence often limit their use at higher—and possibly more effective—doses. Of particular interest is the potential for enhanced analgesic effect with the use of cannabinoids and opioids in combination. Such a combination would allow for opioid analgesic effects to be achieved at lower dosages than are necessary when the opioids are used alone.[1–4] As increasing numbers of patients turn to medicinal cannabis to augment the effects of opioid analgesics, the data on the potential pharmacokinetic interactions and clinical safety of the combination need to be evaluated.

Cannabinoids and opioids share several pharmacologic properties, including antinociception; a tendency to induce hypothermia, sedation, and hypotension; and inhibition of intestinal motility and locomotor activity.[1,5,6] Initially, investigators postulated that cannabinoids and opioids act on the same pathways to produce their pharmacological actions.[7,8] Subsequent preclinical research conducted over the past decade has clarified the nature of the interaction; these data suggest the existence of independent but related mechanisms of antinociception for cannabinoids and opioids.[5]

Synergy in analgesic effects between opioids and cannabinoids has been demonstrated in animal models. The antinociceptive effects of morphine are mediated predominantly by mu opioid receptors but may be enhanced by delta-9-tetrahydrocannabinol (THC) activation of kappa and delta opiate receptors.[8] It has further been suggested that the cannabinoid–opioid interaction may occur at the level of their signal transduction mechanisms.[9,10] Receptors for both classes of drugs are coupled to similar intracellular signaling mechanisms that lead to a decrease in cyclic adenosine monophosphate production via G protein activation.[10–12] There is also some evidence that cannabinoids increase the synthesis and/or release of endogenous opioids.[2,3,12,13]

In addition to these potential pharmacodynamic interactions, there is the potential for pharmacokinetic interaction between cannabinoids and other drugs. Cannabinoids have been shown to affect the kinetics of other drugs in several ways. They inhibit the CYP450-mediated metabolism of some drugs, slow the absorption of others, and may also enhance penetration of some drugs into the brain.[14–16] Our prior study of oral delta-9-THC and smoked cannabis in patients with HIV on protease inhibitor therapies showed that oral THC had no effect on the pharmacokinetics of the antiviral agents.[17] However, smoked cannabis decreased the 8-h area under the plasma concentration–time curve (AUC) of both nelfinavir (−17.4%, $P = 0.46$) and indinavir (−14.5%, $P = 0.07$). In a study involving 24 patients with cancer, cannabis administered as a medicinal tea did not alter the pharmacokinetics of the chemotherapy agents irinotecan and docetaxel.[18]

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Inhalation of vaporized cannabis delivers levels of THC and other cannabinoids similar to those from smoked marijuana but without exposure to combustion products.[19] Here we describe the disposition kinetics of sustained-release morphine and oxycodone, as well as pain ratings and other subjective responses, before and after 4 days of treatment with vaporized cannabis.

RESULTS

Study participants

A total of 315 potential participants were assessed for eligibility between January 2007 and February 2009; most of them were deemed ineligible because they either did not have pain, were not taking the appropriate opioids, or were receiving opioids three times a day. A total of 24 participants were enrolled, 13 of whom were on morphine treatment and 11 on oxycodone. Of those on morphine, 3 participants did not complete the study, leaving 21 evaluable participants (10 on morphine, and 11 on oxycodone) (see **Table 1**). Most of the participants (11 men and 10 women) were white. The average age was 42.9 (range = 33–55) years in the morphine cohort and 47.1 (range = 28–61) years in the oxycodone cohort. The mean morphine dose was 62 mg twice a day (range = 10–200 mg) and the mean oxycodone dose was 53 mg twice a day (range = 10–120 mg). The origin of the participants' pain was musculoskeletal (not otherwise specified) (seven); posttraumatic (four); arthritic (two); peripheral neuropathy (two); cancer, fibromyalgia, migraine, multiple sclerosis, sickle cell disease, and thoracic outlet syndrome (one each).

Pain

Pain ratings on day 1 (before exposure to vaporized cannabis) and on day 5 (after exposure to vaporized cannabis) are shown in **Table 2**. Participants on oxycodone had higher mean pain scores at baseline (mean = 43.8; 95% confidence interval (CI) = 38.6, 49.1) compared with those on morphine (mean = 34.8; 95% CI = 29.4, 40.1). Participants in both groups reported statistically significant reductions in pain ratings on day 5 as compared with day 1. The mean percentage change in pain was statistically significant overall as well as for the patients on morphine, but not for those on oxycodone.

Table 1 Participant characteristics

	Morphine group	Oxycodone group
n	10	11
Women	4	6
Caucasian	8	9
Mean age (range)	42.9 (33–55)	47.1 (28–61)
Mean opioid dose (mg) (range)	62 Twice daily (10–200)	53 Twice daily (10–120)
Mean pain score day 1 (95% CI)	34.8 (29.4, 40.1)	43.8 (38.6, 49.1)

CI, confidence interval.

Opioid disposition kinetics

Mean plasma concentration–time curves for morphine and oxycodone with and without cannabis treatment are shown in **Figure 1**. There was no statistically significant change in the AUC_{12} for either of these opiates (see **Table 3**). There was a statistically significant decrease in maximum concentration (C_{max}) of morphine sulfate during cannabis exposure. The time to C_{max} of morphine tended to be delayed during cannabis treatment, although this effect was not statistically significant. Cannabis had no significant effect on oxycodone kinetics. During cannabis treatment, there were no significant changes in the AUCs of the metabolites of either morphine or oxycodone or in the ratios of individual metabolites to the parent drug.

Plasma THC levels

Mean plasma THC levels were 1.8 ng/ml (SD = 1.5) at baseline, 126.1 ng/ml (SD = 86.2) at 3 min, 33.7 ng/ml (SD = 28.9) at 10 min, 10.9 ng/ml (SD = 9.3) at 30 min, and 6.4 ng/ml (SD = 5.6) at 60 min. The peak THC concentration occurred at 3 min in all the participants. THC plasma levels did not vary significantly by opioid group.

Monitoring of effects

Cannabis inhalation produced a subjective "high" that was not present with the use of opioids alone (see **Figure 2**). In addition, the participants in the morphine cohort felt significantly more stimulated and less hungry on day 5 than on day 1 (see **Table 4**), whereas those in the oxycodone group were less anxious on day 5 as compared with day 1. Other than these, there were no significant changes in the subjective effects measured. No clinically significant adverse events were reported. Pulse oximetry monitoring did not reveal any episodes of lowered oxygen saturation after cannabinoids were added to the participants' stable opioid regimens.

DISCUSSION

Our study findings support preclinical observations that cannabis augments the analgesic effects of opioids. We studied individuals with chronic pain who were taking stable doses of sustained-

Table 2 Pain by study day

		Day 1	Day 5	Difference	Percentage change
	n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Overall	21	39.6 (35.8, 43.3)	29.1 (25.4, 32.8)	−10.7 (−14.4, −7.3)	−27.2 (−45.5, −8.9)
Morphine	11	34.8 (29.4, 40.1)	24.1 (18.8, 29.4)	−11.2 (−16.5, −6.0)	−33.7 (−63.8, −3.5)
Oxycodone	10	43.8 (38.6, 49.1)	33.6 (28.5, 38.6)	−10.3 (−14.8, −5.8)	−21.3 (−47.0, 5.3)

CI, confidence interval.

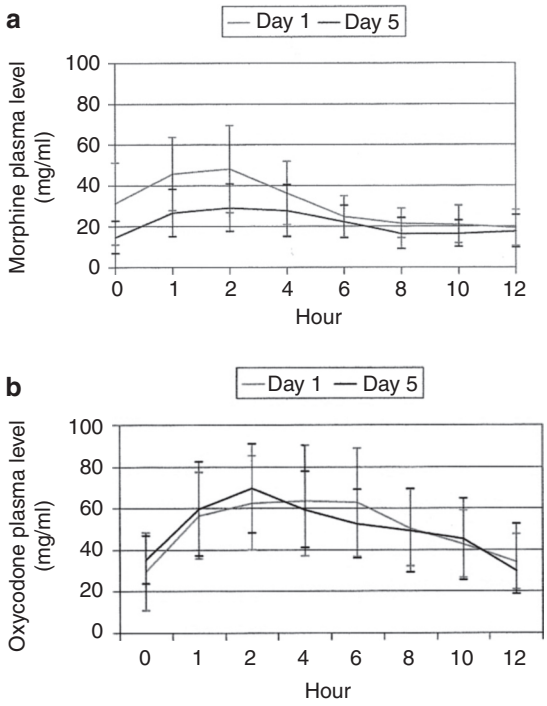

Figure 1 Plasma concentration–time curves for sustained-release (**a**) morphine and (**b**) oxycodone before and after exposure to inhaled cannabis.

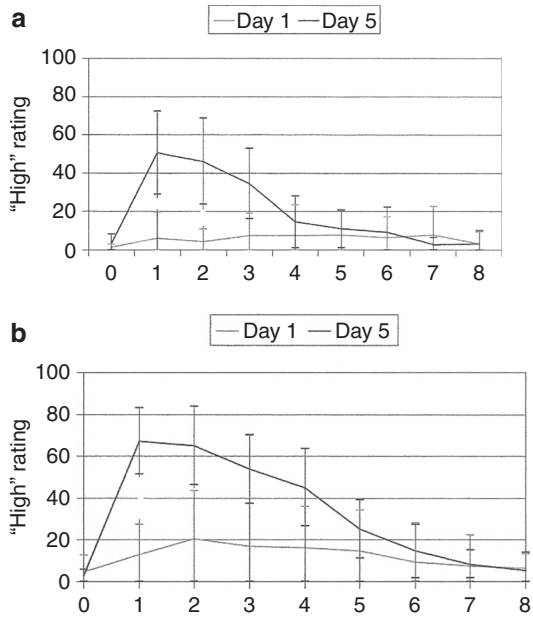

Figure 2 Subjective highs experienced when cannabis was combined with (**a**) morphine and (**b**) oxycodone on day 5.

release morphine or oxycodone. The participants experienced less pain after 5 days of inhaling vaporized cannabis; when the morphine and oxycodone groups were combined, this reduction in pain was significant. This is the first human study to demonstrate that inhaled cannabis safely augments the analgesic effects of opioids. Several other studies have examined the analgesic interaction between oral THC and opioids. Two of those studies involved healthy volunteers exposed to experimental pain conditions.[14,20] THC had little effect in either of the studies, whereas the combination of THC and morphine had synergistic effects on affective responses to pain in one study and on response to electrical stimulation in the other. A placebo-controlled trial in patients taking opioids for chronic pain found that oral dronabinol (delta-9-THC) decreased pain significantly.[15]

The mechanism by which cannabis augments the analgesic effects of opioids could be pharmacokinetic and/or pharmacodynamic. Cannabinoids have been shown to inhibit the metabolism of certain other drugs, both *in vitro* and *in vivo*.[16,21,22] THC has been shown to slow gastrointestinal motility, resulting in the slowing of absorption of orally administered drugs such as pentobarbital and ethanol. THC has also been shown to slow the intranasal absorption of cocaine.[23–25] In animals, cannabinoids have been shown to enhance the uptake of drugs, including cocaine and phencyclidine, into the brain; however, the mechanisms involved are not fully understood.[26]

In the present study, we examined the effects of vaporized cannabis administered three times a day on the steady-state pharmacokinetics of sustained-release morphine and oxycodone administered at 12-h intervals. In the case of morphine, we found that cannabis treatment was associated with a significant decrease in the maximal concentration. On average, the time to maximal morphine concentration was longer during cannabis administration, although this effect was not significant. There were no significant effects of cannabis treatment on the AUCs of morphine's metabolites or on the ratios of metabolites to parent morphine, indicating that cannabis had no effects on metabolic pathways. Vaporized cannabis had no significant effect on oxycodone kinetics or metabolite levels. The finding of a lower maximal concentration of morphine without any accompanying changes in metabolite levels during cannabis treatment is probably due to delayed absorption of morphine, presumably because of slowed gastrointestinal motility. Why such an effect was not seen for oxycodone is not clear. From the pharmacokinetic findings, it is clear that the observed augmentation of analgesia by cannabis cannot be explained on the basis of inhibition of morphine or oxycodone metabolism leading to higher plasma levels of these drugs.

Our findings suggest that cannabis augments opioid analgesia through a pharmacodynamic mechanism. However, prior research in rodents has shown that THC and cannabidiol enhance the penetration of certain other drugs, including cocaine and phencyclidine, into the brain.[26] If cannabinoids also enhance opioid penetration into the brain in humans, this might constitute a pharmacokinetic mechanism for enhancing the analgesic effects of opioids.

The participants reported a subjective high after inhaling cannabis, with little or no high after taking the oral opioids alone. Although we do not have data on the high in these participants in the absence of opioids (that is, with cannabis alone), the magnitude and time course of the high in the participants in the morphine group were similar to our observations in a previous study of inhaled cannabis in healthy subjects.[19] The high in the oxycodone group after cannabis treatment appeared to be more sustained than that in the morphine group, and also as compared with that of our previously studied healthy subjects.

Table 3 Morphine, oxycodone, and their metabolites: mean AUC and CV by study day

	Day 1			Day 5			Day 5/day 1			
	n	Geometric mean	CV	*n*	Geometric mean	CV	Ratio	95% CI	*P* value	
									Par	N-par
Morphine and its metabolites										
Morphine										
T_{max}[a]	10	3.1		10	4.74		1.64	−1.01, 4.30	0.19	0.2
C_{max}	10	43.68	15.95	10	29.66	15.74	0.9	0.85, 0.95	**0.003**	**0.002**
AUC	10	42.01	18.7	10	32.23	15.23	0.95	0.84, 1.05	0.17	0.23
M3g										
C_{max}	10	1,123.94	6.89	10	887.14	4.56	0.97	0.93, 1.00	0.06	0.08
AUC	10	821.39	9.54	10	756.73	7.41	1	0.92, 1.07	0.74	1
M6g										
C_{max}	10	188.67	16.28	10	153.22	6.53	0.97	0.92, 1.01	0.11	0.16
AUC	10	128.25	10.41	10	130.45	10.94	1.02	0.90, 1.15	0.95	0.85
M3g/morphine	10	6.32	17.66	10	6.92	6.92	1.06	0.98, 1.15	0.23	0.19
M6g/morphine	10	3.79	22.69	10	4.13	4.13	1.09	0.98, 1.21	0.25	0.08
Oxycodone and its metabolites										
Oxycodone										
T_{max}[a]	11	3.63		11	2.52		−1.11	−3.66, 1.43	0.35	0.9
C_{max}	11	64.91	12.87	11	62.74	16.67	0.99	0.89, 1.10	0.84	1
AUC	11	76.86	13.38	11	58.67	19.18	0.94	0.84, 1.04	0.18	0.32
Noroxycodone										
C_{max}	11	52.72	14.69	11	65.17	11.78	1.07	0.96, 1.17	0.22	0.46
AUC	11	38.67	15.1	11	36.97	17.11	1.01	0.85, 1.16	0.86	0.7
Oxymorphone										
C_{max}	11	1.42	203.31	11	1.39	175.91	0.15	−1.67, 1.96	0.9	0.82
AUC	10	1.32	334.96	10	1.25	302.37	0.63	0.00, 1.26	0.78	0.77
Noroxycodone/oxycodone	11	2.34	18.33	11	2.49	21.91	1.09	0.93, 1.25	0.31	0.37
Oxymorphone/oxycodone	10	1.07	328.32	10	1.05	354.88	0.7	−0.01, 1.41	0.63	0.63

Statistically significant values are in bold face. AUC, area under the plasma concentration–time curve; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; M3g, morphine-3-glucuronide; M6g, morphine-6-glucuronide; N-par, nonparametric; Par, parametric; T_{max}, time to maximum concentration.

[a]T_{max} values are expressed as arithmetic means on each study day with standard deviation as the measure of variance. Comparisons of T_{max} values on day 1 and day 5 are expressed as the paired difference in these values (day 5 – day 1).

Our study has some limitations. The number of participants was relatively small, although we were powered to detect a 25% change in the 12-hour AUC (AUC_{12}). With respect to pain assessment, our study was not placebo-controlled, and therefore we cannot rule out the possibility that cannabis-enhanced analgesia was a placebo effect or a time effect of changes in activity levels associated with confinement in the inpatient research ward setting throughout the duration of the study. The intervention we used was vaporized cannabis, which delivers levels of THC and other cannabinoids similar to those of smoked cannabis without exposing the user to the combustion products of cannabis cigarettes, which could affect the metabolism and pulmonary uptake of other drugs. Oral cannabis is commonly used to deliver medicinal THC and results in high first-pass levels of cannabinoids in the liver, which could have effects on opioid metabolism different from those caused by vaporized cannabis. Therefore, further research is needed to determine how different cannabis delivery systems affect the metabolism of opioids and other drugs.

In conclusion, we found that vaporized cannabis augments analgesia in individuals with chronic pain on a treatment regimen of stable doses of sustained-release morphine or oxycodone, and that the mechanism of augmentation is not explained by elevation of plasma opioid concentrations or inhibition of opioid metabolism. Cannabis appears to slow morphine absorption such that maximal concentrations for a dosing interval are lower. The effect of inhaled cannabis in enhancing opiate analgesia is most likely achieved through a pharmacodynamic mechanism. These results suggest that further controlled studies of the synergistic interaction between cannabinoids and opioids are warranted.

Table 4 Subjective effects: morphine vs. morphine/cannabis and oxycodone vs. oxycodone/cannabis

	Day 1			Day 5			Day 5 – day 1		
	n	Mean	SD	*n*	Mean	SD	Difference	95% CI	*P* value
Morphine vs. morphine/cannabis									
Like effect									
C_{max}	9	54.56	24.38	10	63.5	29	6.89	−8.49, 22.26	0.33
AUC	10	2.99	2.99	10	2.01	1.2	−0.98	−3.00, 1.04	0.3
High									
C_{max}	10	13.6	24.57	10	54.7	30.76	41.1	20.85, 61.35	**0.001**
AUC	10	0.74	1.44	10	1.96	1.25	1.22	0.24, 2.20	**0.02**
Stimulated									
C_{max}	10	11.7	23.24	10	37.6	31.91	25.9	9.03, 42.77	**0.007**
AUC	10	0.55	1.08	10	1.5	1.6	0.96	−0.10, 2.01	0.07
Anxious									
C_{max}	10	31.8	27.84	10	27.4	29.33	−4.4	−25.12, 16.32	0.64
AUC	10	1.73	1.84	10	1.29	2.01	−0.44	−2.02, 1.14	0.54
Sedated									
C_{max}	10	36.9	32.42	10	36.5	24.67	−0.4	−21.64, 20.84	0.97
AUC	10	2.75	2.89	10	1.74	1.47	−1.01	−3.03, 1.00	0.29
Hungry									
C_{max}	10	64.8	34.57	10	42	29.44	−22.8	−44.71, −0.89	**0.04**
AUC	10	2.89	2.3	10	1.34	1.28	−1.55	−3.09, −0.02	**0.05**
Dry mouth									
C_{max}	10	32	22.97		25.8	30.75	−6.2	−31.82, 19.42	0.6
AUC	10	2.29	2.34	10	1.28	2.13	−1.01	−3.16, 1.15	0.32
Oxycodone vs. oxycodone/cannabis									
Like effect									
C_{max}	11	62.91	30.03	11	78.27	17.84	15.36	−3.14, 33.86	0.09
AUC	11	2.92	1.74	11	3.21	1.49	0.29	−0.69, 1.28	0.52
High									
C_{max}	11	23.73	29.35	11	72.73	23.22	49	27.82, 70.18	**0.001**
AUC	11	0.96	0.91	11	3.47	1.58	2.5	1.65, 3.36	**0.001**
Stimulated									
C_{max}	11	32.64	32.09	11	30	28.42	−2.63	−23.05, 17.77	0.78
AUC	11	1.21	1.12	11	1.76	2.27	0.55	−0.76, 1.87	0.37
Anxious									
C_{max}	11	49.73	34.04	11	33.39	33.39	−16.45	32.02, 0.89	**0.04**
AUC	11	2.22	1.87	11	1.88	1.88	−0.55	−1.55, 0.46	0.26
Sedated									
C_{max}	11	37.18	32.46	11	30.74	30.74	14.73	−10.06, 39.51	0.22
AUC	11	1.67	1.51	11	1.38	1.38	0.57	−0.96, 2.10	0.42
Hungry									
C_{max}	11	61.18	24.12	11	28.56	28.56	4.1		0.92
AUC	11	3.27	2.33	11	2.15	2.15	−0.5	−2.46, 1.45	0.58
Dry mouth									
C_{max}	11	22.18	19.6	11	33.65	33.65	23.45	−7.38, 54.29	0.12
AUC	11	1	1.07	11	1.32	1.32	0.6	−0.77, 7.97	0.35

Statistically significant values are in bold face. AUC, area under the plasma concentration–time curve; CI, confidence interval; C_{max}, maximum concentration.

METHODS

Study participants. The participants were adults >18 years of age who were experiencing chronic pain and receiving ongoing analgesic therapy with sustained-release morphine sulfate (MS Contin) or oxycodone hydrochloride (OxyContin) every 12 h. The participants were required to have been on a stable medication regimen for at least 2 weeks prior to the commencement of the study. Hepatic transaminase levels were required to be within 5 times the upper limit of normal and serum creatinine to be <2.0 mg/dl (177 μmol/l). A negative pregnancy test was required for female participants. Exclusion criteria included severe coronary artery disease, uncontrolled hypertension, cardiac ventricular conduction abnormalities, orthostatic mean blood pressure drop of >24 mm Hg, severe chronic obstructive pulmonary disease, history of renal or hepatic failure, active substance abuse, neurologic dysfunction or psychiatric disorder severe enough to interfere with assessment of pain, current use of smoked tobacco products or a confirmed cotinine level, and, in women, pregnancy, breastfeeding, or not using adequate birth control.

All the participants were required to have prior experience of smoking cannabis (six or more times in their lifetime) so that they would know how to inhale and what neuropsychologic effects to expect. Current users were asked to discontinue cannabis use for 30 days prior to commencement of the study, and such abstention was confirmed by a negative urine THC assay prior to study enrollment.

The study was approved by the institutional review board at the University of California, San Francisco; the Research Advisory Panel of California; the Drug Enforcement Administration; the US Food and Drug Administration, and the National Institute on Drug Abuse. Written informed consent was obtained from all the participants. The ClinicalTrials.gov registration number was NCT00308555.

Study medication. The National Institute on Drug Abuse provided cannabis in the form of cigarettes weighing 0.9 g on average and containing 3.56% delta-9-THC. The cigarettes were kept in a locked freezer with an alarm device attached until they were dispensed to a locked freezer in the San Francisco General Hospital Clinical Research Center where the inpatient study was conducted. The frozen cigarettes were thawed and rehydrated overnight in a humidifier. The cannabis was removed from the prerolled cigarettes and administered in a Volcano vaporizer (Model #0100 CS; Tuttlingen, Germany), heated to 190 °C.[27] The study participants were housed in a room with a fan ventilating to the outside. To maximize standardization of the vaporized doses, the subjects followed a uniform puffing procedure: the cannabis was inhaled for 5 s and then held for 10 s, with a 45-s pause before a repeat inhalation.[28] The participants were encouraged to inhale the entire vaporized dose of 0.9 g of 3.56% delta-9-THC or as much as they could tolerate.

In a previous study we had demonstrated that this vaporization procedure results in plasma THC levels similar to those induced by smoked marijuana but without significant exposure to carbon monoxide and other combustion products.[19]

Opioid disposition kinetics. Opioid pharmacokinetics were determined on days 1 and 5 from blood samples drawn at baseline and again at 1, 2, 4, 6, 8, 10, and 12 h after oral opioid administration. Given that the opioids were administered every 12 h, these measurements represent plasma concentration levels at steady state. On day 5, in addition to the opioid pharmacokinetics samples, THC plasma levels were measured at baseline and at 3, 10, 30, and 60 min to determine THC exposure for purposes of comparison with findings of prior and future studies. Our previous studies had demonstrated that this time course encompasses most of the THC AUC.[19]

The main outcome measure was the AUC_{12} for morphine and its glucuronide metabolites, or for oxycodone and its major metabolites, oxymorphone and noroxycodone.

Samples were shipped in a frozen state to the Center for Human Toxicology at the University of Utah, where they were analyzed for cannabinoids, morphine, and oxycodone using published procedures. Briefly, morphine, morphine-3-glucuronide, and morphine-6-glucuronide were measured using liquid chromatography with electrospray ionization–tandem mass spectrometry, with lower limits of quantification of 0.50 and 0.25 ng/ml for morphine and the glucuronides, respectively.[29] Oxycodone, oxymorphone, and noroxycodone were measured using liquid chromatography with electrospray ionization–tandem mass spectrometry, with lower limits of quantification of 0.2 ng/ml for all analytes.[30]

Cannabinoid measurements were obtained using a combination of modifications of previously published methods. The samples underwent liquid–liquid extraction,[31] and both extracts were combined and then derivatized and analyzed as previously described,[32] except that the method was modified to suit a different instrument (i.e., a Hewlett Packard 5890 GC (Palo Alto, CA) equipped with a DB-5 MS, 30 m × 0.25 mm, 0.25-mm column and interfaced with a Finnigan MAT SSQ 7000 MS (San Jose, CA) in negative chemical ionization mode).

Effects monitoring. Objective and subjective effects were measured to assess whether vaporized cannabis increases or attenuates the side effects associated with opioid analgesics. Subjective effects were assessed via participants' self-reports using the Drug Effects Questionnaire administered before the morning opioid dose and again at 30 min and 1, 2, 4, 6, 8, 10, and 12 h after drug administration on days 1 and 5. This questionnaire records subjective findings using standard visual analog scales where 0 is "no effect" and 100 is "maximal effect."[33] Assessment of drug effects included pain, stimulation, anxiety, sedation, feeling "down," hunger, mellowness, confusion, irritation, depression, feeling withdrawn, dizziness, nausea, and dryness of the mouth. In addition, the subjects were evaluated by the nursing staff for side effects every 4 h, recording scores for anxiety, sedation, disorientation, paranoia, confusion, dizziness, nausea, urinary retention, constipation, emesis, headache, swollen extremities, twitching, excitement, and level of consciousness on a scale from 0 to 4. The participants were monitored daily for nausea and vomiting using the Rhodes Index of Nausea, Vomiting, and Retching Questionnaire.[34] Because there was a concern that enhanced opioid effects could lead to respiratory depression, continuous pulse oximetry was performed every night, with the results documented every 2 h on the nursing flowsheet.

Statistical analysis.

Sample size: In a published study of individuals who took morphine on an empty stomach, the standard deviation of the within-person change in log (AUC_{10}) for a morphine solution was 20% over the course of 12 months.[35] Using this information, we estimated that, with a sample of 10 subjects, the study would have 80% power to detect a 25% percent change in the AUC_{12} between days 1 and 5. This estimate was based on a standardized effect size (E/S) of 1.25, using an alpha of 0.05, where E is the within-subject effect size (25%) and S is the standard deviation of the mean of the paired differences (20%) using a paired *t*-test.[36,37] In prior pharmacokinetics studies, a 30% change in AUC was thought to be clinically significant.[38] Therefore, we set the target size at 25% to ensure that we would be able to capture a clinically significant change in AUC_{12}. We enrolled at least 10 participants in each of the two (morphine and oxycodone) groups.

Data analysis: We described the characteristics of the participants at study entry overall and within each opioid group. We presented the mean (with 95% CI) plasma levels for each opioid over the 12-h observation period on days 1 and 5.

The primary outcome was the change in the AUC_{12} for morphine or oxycodone before and after cannabis exposure. We standardized plasma levels for each opioid to doses of 60 mg b.i.d. (observed opioid plasma level × (60 mg/administered opioid dose)). The standardized AUC_{12} was derived using the trapezoidal method over the dosing interval. We estimated the geometric mean and coefficient of variation in

the standardized AUC on days 1 and 5. We then computed the ratio of the geometric means (with 95% CI) for day 5/day 1. We tested the hypothesis of a statistically significant change in standardized AUC_{12} of at least 25%, using paired *t*-tests and nonparametric Wilcoxon signed-rank tests. We also assessed the percentage change in the geometric mean for C_{max} and the arithmetic mean for time to maximum concentration from the plasma concentration-vs.-time data for each subject. We used similar methods to describe results and assess changes for plasma concentrations of the metabolites of morphine (morphine-3-glucuronide and morphine-6-glucuronide) and oxycodone (oxymorphone and noroxycodone). We assessed the mean THC plasma levels (with 95% CIs) for a duration of 1 h, for the participants overall as well as by opioid group.

We described the mean pain ratings on days 1 and 5, both overall and within each opioid group, using mean values and 95% CIs. We assessed the mean values (with 95% CI) of individual differences and percentage changes in pain between days 1 and 5, both overall and within each opioid group, using paired *t*-tests.

Next, we assessed the subjective effects of vaporized marijuana among these participants. We represented the mean perceived high over the dosing period on days 1 and 5 for each opioid group. In addition, we estimated the mean value (with 95% CI) of each subjective effect on days 1 and 5 and determined statistically significant changes in the mean values (with 95% CI) of individual differences, using paired *t*-tests for each opioid group.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Cannabis in Cancer Care

DI Abrams[1] and M Guzman[2]

Cannabis has been used in medicine for thousands of years prior to achieving its current illicit substance status. Cannabinoids, the active components of *Cannabis sativa*, mimic the effects of the endogenous cannabinoids (endocannabinoids), activating specific cannabinoid receptors, particularly CB1 found predominantly in the central nervous system and CB2 found predominantly in cells involved with immune function. Delta-9-tetrahydrocannabinol, the main bioactive cannabinoid in the plant, has been available as a prescription medication approved for treatment of cancer chemotherapy-induced nausea and vomiting and anorexia associated with the AIDS wasting syndrome. Cannabinoids may be of benefit in the treatment of cancer-related pain, possibly synergistic with opioid analgesics. Cannabinoids have been shown to be of benefit in the treatment of HIV-related peripheral neuropathy, suggesting that they may be worthy of study in patients with other neuropathic symptoms. Cannabinoids have a favorable drug safety profile, but their medical use is predominantly limited by their psychoactive effects and their limited bioavailability.

Although long recognized for its medicinal values and widely used by millions throughout the world, cannabis receives little attention in the standard literature because of its status as a controlled substance and classification in the United States as a Schedule I agent with a high potential for abuse and no known medical use. Data on the potential effectiveness of medicinal cannabis is difficult to find due to the limited numbers of clinical trials that have been conducted to date. As a botanical, cannabis shares those difficulties encountered in the study of plants that are grown in many climates and environments from diverse genetic strains and harvested under variable conditions.

CANNABIS AS MEDICINE: A BRIEF HISTORY

The use of cannabis as medicine dates back nearly 3,000 years.[1] Employed widely on the Indian subcontinent, cannabis was introduced into Western medicine in the 1840s by W.B. O'Shaughnessy, a surgeon who learned of its medicinal benefits first-hand while working in the British East Indies Company. Promoted for reported analgesic, sedative, antiinflammatory, antispasmodic, and anticonvulsant properties, cannabis was said to be the treatment of choice for Queen Victoria's dysmennorhea. In the early 1900s, medicines that were indicated for each of cannabis' purported activities were introduced into the Western armamentarium, making its use less widespread.

Physicians in the United States were the main opponents to the introduction of the Marihuana Tax Act by the Treasury Department in 1937. The legislation was masterminded by Harry Anslinger, director of the Federal Bureau of Narcotics from its inception in 1931 until 1962, who testified in Congress that "Marijuana is the most violence-causing drug in the history of mankind." The Act imposed a levy of one dollar an ounce for medicinal use and one hundred dollars an ounce for recreational use, which in 1937 dollars was a prohibitive cost. By using the Mexican name for the plant and associating it with nefarious South-of-the-Border activities, the proponents fooled many physicians. The Act was singly opposed by the American Medical Association, who felt that objective evidence that cannabis was harmful was lacking and that its passage would impede further research into its medical utility. In 1942, cannabis was removed from the U.S. Pharmacopoeia. In 1970, with the initiation of the Controlled Substances Act, marijuana was classified as a Schedule I drug. Where both Schedule I and Schedule II substances have a high potential for abuse, Schedule I drugs are distinguished by having no accepted medical use. Other Schedule I substances include heroin, LSD, mescaline, methylqualone, and, most recently, gammahydroxybutyrate (GHB). Despite efforts to change the scheduling of cannabis, it remains a Schedule I substance at this time.

Delta-9-THC is one of the ~100 cannabinoids found in the cannabis plant and is felt to be the main psychoactive component. Overall, the plant contains about 400 compounds derived from its secondary metabolism, many of which may contribute to its medicinal effect. Synthetic delta-9-THC in sesame oil (dronabinol, Marinol) was first licensed and approved in 1986 for the

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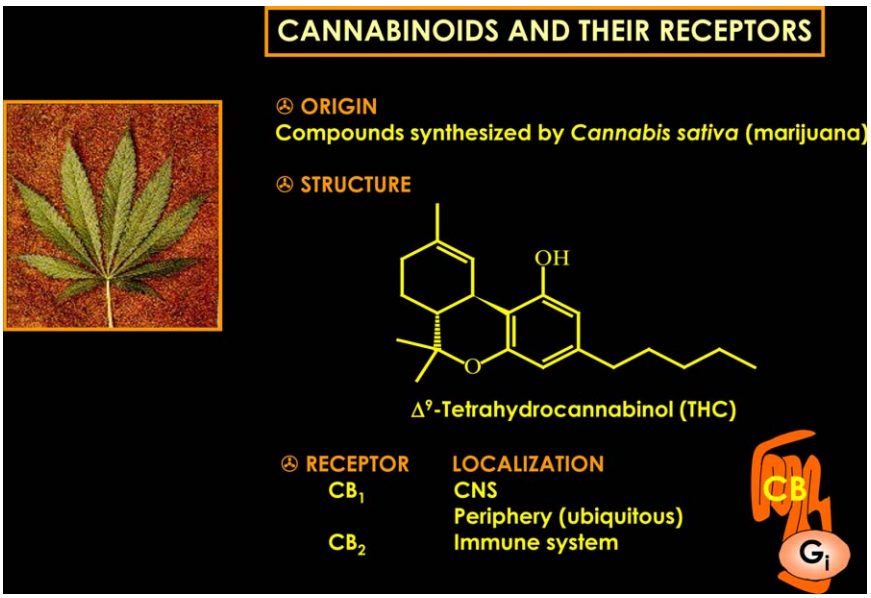

Figure 1 Cannabinoids are a group of 21 carbon terpenophenolic compounds produced by *Cannabis* species. The phytocannabinoids complex with two receptors, CB1 and CB2, to produce their physiologic effects.

treatment of chemotherapy-associated nausea and vomiting. Clinical trials done at the time determined that dronabinol was as effective, if not more so, than the available antiemetic agents.[2] Dronabinol was investigated for its ability to stimulate weight gain in patients with the AIDS wasting syndrome in the late 1980s. Results from a number of trials suggested that although patients reported an improvement in appetite, no statistically significant weight gain was appreciated.[3,4] Nabilone (Cesamet) is another synthetic delta-9-THC that is also available by prescription. More recently, nabiximols (Sativex), a whole plant extract delivered as an oromucosal spray, has been developed and approved for medical use in Europe and Canada. This article will review the biology and pharmacology of cannabis and cannabinoids and focus on their use in symptom management, particularly in patients with cancer.

CANNABINOID CHEMISTRY AND BIOLOGIC EFFECTS

Cannabinoids are a group of 21 carbon terpenophenolic compounds produced uniquely by *Cannabis sativa* and *Cannabis indica* species.[1] With the discovery of endogenous cannabinoids and to distinguish them from pharmaceutical compounds, the plant compounds may also be referred to as phytocannabinoids. Although delta-9-THC is the primary active ingredient in cannabis, there are a number of non-THC cannabinoids and noncannabinoid compounds that also have biologic activity. Cannabidiol (CBD), cannabinol, cannabichromene, cannabigerol, tetrahydrocannabivirin, and delta-8-THC are just some of the additional cannabinoids that have been identified. It is postulated that the secondary compounds may enhance the beneficial effects of delta-9-THC, for example by modulating the THC-induced anxiety, anticholinergic, or immunosuppressive effects, and may reduce the unwanted effects of delta-9-THC, for example by attenuating seizures, psychoses, or motor discoordination. In addition, cannabis-associated terpenoids and flavonoids may increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens, and provide antiinflammatory activity.[1,5]

The neurobiology of the cannabinoids has only been identified within the past 25 years, during which time an explosion of knowledge has occurred.[1] In the mid-1980s, researchers developed a potent cannabinoid agonist to be used in research investigations. In 1986 it was discovered that cannabinoids inhibited the accumulation of 3′-5′ cyclic adenosine monophosphate (cAMP), suggesting the presence of a receptor-mediated mechanism. By attaching a radiolabel to the synthetic cannabinoid, the first cannabinoid receptor, CB1, was pharmacologically identified in the brain in 1988. The CB1 receptor is coupled to G_i proteins (**Figure 1**). Its engagement inhibits adenylyl cyclase and voltage-gated calcium channels, and stimulates rectifying potassium conductances and mitogen-activated protein kinase cascades. By 1990, investigators had cloned the CB1 receptor, identified its DNA sequence, and mapped its location in the brain, with the largest expression being in the basal ganglia, cerebellum, hippocampus, and cerebral cortex. Nowadays, CB1 is known to be a ubiquitous protein that is present in basically all body tissues. In 1993 a second cannabinoid receptor, CB2, was identified outside the brain. Originally detected in macrophages and the marginal zone of the spleen, the highest abundance of CB2 receptors is located on the B lymphocytes and natural killer cells, suggesting a role in immunity.

The existence of cannabinoid receptors has subsequently been demonstrated in most animal species, all the way down to invertebrates. Are these receptors present in the body solely to complex with ingested phytocannabinoids? The answer came in 1992 with the identification of a brain constituent that binds to the cannabinoid receptor. Named anandamide from the Sanskrit word for bliss, the first endocannabinoid had been discovered.

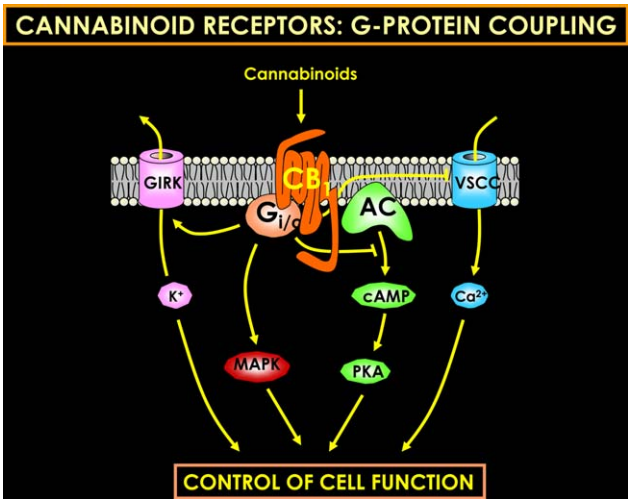

Figure 2 Signaling pathways coupled to the CB_1 cannabinoid receptor. Cannabinoids exert their effects by binding to specific G_i protein-coupled receptors. The CB_1 cannabinoid receptor signals to a number of different cellular pathways. These include, for example, (i) inhibition of the adenylyl cyclase (AC)cyclic AMPprotein kinase A (PKA) pathway; (ii) modulation of ion conductances, by inhibition of voltage-sensitive Ca^{2+} channels (VSCC) and activation of G_i protein-coupled inwardly rectifying K^+ channels (GIRK); and (iii) activation of mitogen-activated protein kinase (MAPK) cascades. Other less established cannabinoid receptor effectors and the crosstalk among the different pathways have been omitted for simplification.

Subsequently, 2-arachidonoylglycerol (2-AG) has also been confirmed as part of the body's endogenous cannabinoid system. These endocannabinoids function as neuromodulators. As the ligands for the 7-transmembrane domain cannabinoid receptors located in presynaptic nerve terminals, binding of the endocannabinoid leads to G-protein activation and the cascade of events transpires resulting in the opening of potassium channels, which decreases cell firing and the closure of calcium channels that decreases neurotransmitter release (**Figure 2**).

The functions of the endogenous cannabinoid system in the body are becoming more appreciated through advances in cannabinoid pharmacology.[6,7] The identification of the cannabinoid receptors has led to a host of agonists and antagonists being synthesized. Utilizing these tools, investigators are discovering that the system is likely to be important in the control of many biological functions, such as modulation of pain and appetite, suckling in the newborn, and the complexities of memory, to mention just a few. In addition to being utilized to learn more about the natural function of the endocannabinoid system, a number of these cannabinoid receptor agonists and antagonists are being developed as potential pharmaceutical therapies. In the meantime, dronabinol, nabilone, and cannabis are the currently available cannabinoid therapies in the US. Levonantradol (Nantrodolum) is a synthetic cannabinoid administered intramuscularly, not used as much clinically since the oral agents became available. Nabiximols, a standardized whole-plant extract delivered as an oromucosal spray with an ~1:1 ratio of THC and cannabidiol, is available in Canada and some European countries and is undergoing late-phase testing in the US and other countries.

Through the receptors described above, cannabis delivered by way of inhalation, orally, or oromucosally can produce a host of biologic effects.[8] The 1999 Institute of Medicine report, Marijuana and Medicine: Assessing the Science Base, makes the following general conclusions about the biology of cannabis and cannabinoids.[9]

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multifaceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research has demonstrated the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals but appear mild compared with those of withdrawal from opiates or benzodiazepines.

PHARMACOLOGY OF CANNABIS

When taken by mouth, there is a low (6–20%) and variable oral bioavailability.[1,8] Peak plasma concentrations occur after 1–6 hours and remain elevated with a terminal half-life of 20–30 hours. When consumed orally, delta-9-THC is initially metabolized in the liver to 11-OH-THC, also a potent psychoactive metabolite. On the other hand, when inhaled, the cannabinoids are rapidly absorbed into the bloodstream with a peak concentration in 2–10 minutes that rapidly declines over the next 30 minutes. Inhalation thus achieves a higher peak concentration with a shorter duration of effect. Less of the psychoactive 11-OH-THC metabolite is formed. When nabiximols is taken oromucosally, no pharmacokinetic interactions seem to occur between its two major cannabinoid constituents: THC and CBD, and the pharmacokinetic properties of the THC present in nabiximols are similar to those of oral THC.[10]

Cannabinoids can interact with the hepatic cytochrome P450 enzyme system.[1] CBD, for example, can inactivate CYP3A4. After repeated doses, some of the cannabinoids may induce P450 isoforms. The effects are predominantly related to the CYP1A2, CYP2C, and CYP3A isoforms. The potential for a cannabinoid interaction with cytochrome P450 and, hence, possibly metabolism of pharmaceutical agents has led to a small amount of data on the possibility of botanical:drug interactions. For example, in one study 24 cancer patients were treated with intravenous irinotecan (600 mg, $n = 12$) or docetaxel (180 mg, $n = 12$), followed 3 weeks later by the same drugs concomitant with medicinal cannabis taken as an herbal tea for 15 consecutive days, starting 12 days before the second treatment.[11] The carefully conducted pharmacokinetic analyses showed that cannabis administration as a tea did not significantly influence exposure to and clearance of irinotecan or docetaxel.

CANNABINOIDS AND CANCER SYMPTOM MANAGEMENT

Antiemetic effect

The nausea and vomiting related to cancer chemotherapy continues to be a significant clinical problem even in light of the newer

agents that have been added to our armamentarium since the 1970s and 1980s, when clinical trials of cannabinoids were first conducted.[12] In those days, phenothiazines and metoclopramide were the main antiemetic agents used. Dronabinol (synthetic THC) and nabilone (a synthetic analog of THC) were both tested as novel oral agents in a number of controlled clinical trials. Nabilone was approved in Canada in 1982, but only recently became available in the US. Dronabinol was approved as an antiemetic to be used in cancer chemotherapy in the US in 1986.

Numerous meta-analyses confirm the utility of these THC-related agents in the treatment of chemotherapy-induced nausea and vomiting. Tramer *et al.* [13] conducted a systematic review of 30 randomized comparisons of cannabis with placebo or antiemetics from which dichotomous data on efficacy and harm were available. Oral nabilone, oral dronabinol, and intramuscular levonantradol were tested. No smoked cannabis trials were included. In all, 1,366 patients were involved in the systematic review. Cannabinoids were found to be significantly more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride. In this analysis, the number of people needed to treat for one person to have an effect (NNT) for complete control of nausea was 6; the NNT for complete control of vomiting was 8. Cannabinoids were not more effective in patients receiving very low or very high emetogenic chemotherapy. In crossover trials, patients preferred cannabinoids for future chemotherapy cycles. Tramer *et al.* identified some "potentially beneficial side effects" that occurred more often with cannabinoids including the "high," sedation, or drowsiness, and euphoria. Less desirable side effects that occurred more frequently with cannabinoids included dizziness, dysphoria, or depression, hallucinations, paranoia, and hypotension.

A later analysis by Ben Amar[14] reported that 15 controlled studies had compared nabilone to placebo or available antiemetic drugs. In 600 patients with a variety of malignant diagnoses, nabilone was found to be superior to prochlorperazine, domperidone, and alizapride, with patients clearly favoring nabilone for continuous use. Nabilone has also been shown to be moderately effective in managing the nausea and vomiting associated with radiation therapy and anesthesia after abdominal surgery.[13,15] In the same meta-analysis, Ben Amar reported that in 14 studies of dronabinol involving 681 patients, the cannabinoid antiemetic effect was equivalent or significantly greater than chlorpromazine and equivalent to metochlopramide, thiethylperazine, and haloperidol. It is noted that the efficacy of the cannabinoids in these studies was sometimes outweighed by the adverse reactions and that none of the comparator antiemetics were of the serotonin receptor antagonist class that is the mainstay of treatment today.

A small pilot, randomized, double-blind, placebo-controlled phase II trial was conducted to investigate the whole-plant cannabis-based medicine, nabiximols, added to standard antiemetics in the treatment of chemotherapy-induced nausea and vomiting.[16] Seven patients were randomized to receive the mixture of delta-9-THC and CBD, and nine added placebo to their standard of care antiemetic regimen. Five of the seven nabiximols recipients compared to two of the nine on placebo experienced a complete response with a mean daily dose of 4.8 sprays (~13 mg THC and 12 mg CBD) in both groups without serious adverse effects. Further larger studies of the potential of nabiximols as an antiemetic are warranted.

There have been only three controlled trials evaluating the efficacy of smoked cannabis in chemotherapy-induced nausea and vomiting.[14] In two of the studies, the smoked cannabis was only made available after patients failed dronabinol. The third trial was a randomized, double-blind, placebo-controlled, crossover trial involving 20 adults where both smoked cannabis and oral THC were evaluated. One-quarter of the patients reported a positive antiemetic response to the cannabinoid therapies. On direct questioning of the participants, 35% preferred the oral dronabinol, 20% preferred the smoked marijuana, and 45% did not express a preference. Four participants receiving dronabinol alone experienced distorted time perception or hallucinations which were also reported by two with smoked marijuana and one with both substances. Both dronabinol and nabilone are US Food and Drug Administration (FDA)-approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic therapy. Nabilone's extended duration of action allows for twice a day dosing of one or two mg commencing 1–3 hours prior to receiving chemotherapy. A dose of 1 or 2 mg the night before administration of chemotherapy might also be useful. It is recommended to commence dronabinol at an initial dose of 5 mg/m^2, also 1–3 hours prior to the administration of chemotherapy, then every 2–4 hours after chemotherapy, for a total of 4–6 doses/day. Should the 5 mg/m^2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose. Nabilone, with fewer metabolites and a lower dose range, may be associated with fewer side effects. The need to dose 1–3 hours prior to chemotherapy is one factor that drives patients to prefer inhaled cannabis where the delivery and effect peak within minutes. Patients also prefer the ability to more tightly titrate the dose of cannabinoids they receive when inhaling compared to oral ingestion.

The National Comprehensive Cancer Network antiemesis guidelines recommend cannabinoids among other therapies to consider as a breakthrough treatment for chemotherapy-induced nausea and vomiting (http://www.nccn.org).

Appetite stimulation

Anorexia, early satiety, weight loss, and cachexia are some of the most daunting symptom management challenges faced by the practicing oncologist. There are very few tools in the toolbox for addressing these concerns. For many the hormonal manipulation with megestrol acetate (synthetically derived progesterone) may be contraindicated or the side effects undesirable. Two small controlled trials demonstrated that oral THC stimulates appetite and may slow weight loss in patients with advanced malignancies.[14] In a larger randomized, double-blind, parallel group study of 469 adults with advanced cancer and weight loss, patients received either 2.5 mg of oral THC twice daily, 800 mg of oral megestrol daily, or both. In the megestrol monotherapy group, appetite increased in 75% and weight in 11% compared to 49% and 3%, respectively, in the oral THC group. These differences

were statistically significant. The combined therapy did not confer additional benefits. A smaller randomized placebo-controlled trial of dronabinol in cancer patients demonstrated enhanced chemosensory perception in the treatment group.[17] In the patients receiving cannabinoids, food was reported to taste better, appetite improved, and the proportion of protein calories was increased compared to the placebo group.

Many animal studies have previously demonstrated that THC and other cannabinoids have a stimulatory effect on appetite and increase food intake. It is felt that the endogenous cannabinoid system may serve as a regulator of feeding behavior. For example, anandamide in mice leads to a potent enhancement of appetite.[18] It is felt that the CB1 receptors, present in the hypothalamus where food intake is controlled and in the mesolimbic reward system, may be involved in the motivational or reward aspects of eating. This led to the development of the pharmaceutical CB1 antagonist rimonabant (Acomplia), which was approved in Europe for the treatment of obesity on the basis of phase III clinical trials where it was shown to induce a 4–5 kg mean weight loss with improved glycemic and lipid profiles.[19] However, Acomplia was never approved in the US and was ultimately withdrawn from the European market because it was found to induce anxiety and depressive disorders that were deemed high risk, often leading to patient suicide.

Anecdotal as well as clinical trial evidence also supports the appetite-stimulating effect of inhaling cannabis. In classic trials conducted in the 1970s in healthy controls, it was found that, especially when smoked in a social/communal setting, cannabis inhalation led to an increase in caloric intake, predominantly in the form of between-meal snacks, mainly in the form of fatty and sweet foods. In cancer patients with anorexia as well as chemotherapy-induced nausea, it is worth noting that cannabis is the only antiemetic that also has orexigenic action. Although cannabis thus provides two potential benefits to the patient with cancer, the appetite stimulation does not always reverse the cancer cachexia which is a function of energy wasting in addition to decreased food intake. Interestingly, an increasing body of epidemiologic evidence suggests that instead of being overweight, the general noncancer population of cannabis users has a lower prevalence of obesity than nonusers, with smaller waist circumferences and lower fasting insulin levels.[20,21]

Analgesia

Our understanding of the possible mechanisms of cannabinoid-induced analgesia has been greatly increased through study of the cannabinoid receptors, endocannabinoids and synthetic agonists and antagonists. The CB1 receptor is found in the central nervous system as well as in peripheral nerve terminals. Elevated levels of the CB1 receptor, like opioid receptors, are found in areas of the brain that modulate nociceptive processing.[1,22] In contrast, CB2 receptors are located in peripheral tissue and are present at very low expression levels in the central nervous system (CNS). Of the endogenous cannabinoids identified, anandamide has high affinity for CB1 receptors, whereas 2-AG has high affinity for both CB1 and CB2 receptors. With the development of receptor-selective antagonists (for example, SR141716 for CB1 and SR144528 for CB2), additional information has been obtained regarding the roles of the receptors and endogenous cannabinoids in modulation of pain. Where the CB1 agonists exert analgesic activity in the CNS, both CB1 and CB2 agonists have peripheral analgesic actions. Cannabinoids may also contribute to pain modulation through an antiinflammatory mechanism—a CB2 effect with cannabinoids acting on mast cell receptors to attenuate the release of inflammatory agents such as histamine and serotonin and on keratinocytes to enhance the release of analgesic opioids.[23,24]

Cannabinoids are effective in animal models of both acute and persistent pain. The central analgesic mechanism differs from the opioids in that it cannot be blocked by opioid antagonists. The potential for additive analgesic effects with opioids as well as the potential for cannabinoids to reduce nausea and increase appetite make a strong case for the evaluation of marijuana as adjunctive therapy for patients on morphine.[25] Unfortunately, although the medical literature cites evidence of cannabinoids' ability to reduce naturally occurring pain, few human studies have been performed. Early studies of cannabinoids on experimental pain in human volunteers produced inconsistent results. In some cases, the administration of cannabinoids failed to produce observable analgesic effects; in others, cannabinoids resulted in an increase of pain sensitivity (hyperalgesia). Institute of Medicine reviewers noted that these studies suffered from poor design and methodological problems and dubbed their findings inconclusive.[9]

Encouraging clinical data on the effects of cannabinoids on chronic pain come from three studies of cancer pain. Cancer pain results from inflammation, mechanical invasion of bone or other pain-sensitive structure, or nerve injury. It is severe, persistent, and often resistant to treatment with opioids. Noyes *et al.*[26] conducted two studies on the effects of oral THC on cancer pain. Both studies used standard single-dose analgesic study methodology and met the criteria for well-controlled clinical trials of analgesic efficacy. The first trial measured both pain intensity and pain relief in a double-blind, placebo controlled study of 10 subjects. Observers compared the effects of placebo and 5, 10, 15, and 20 mg doses of delta-9-THC over a 6-hour period. Researchers reported that 15 and 20 mg doses produced significant analgesia, as well as antiemesis and appetite stimulation. The authors cautioned that some subjects reported unwanted side effects such as sedation and depersonalization at the 20 mg dose level. In a follow up single-dose study of 36 subjects, Noyes *et al.*[27] reported that 10 mg of THC produced analgesic effects over a 7-hour observation period comparable to 60 mg of codeine, and that 20 mg of THC induced effects equivalent to 120 mg of codeine. The authors noted that respondents found higher doses of THC to be more sedative than codeine. However, in a separate publication, Noyes and Baram[28] reported that patients administered THC had improved mood, sense of well-being, and less anxiety.

A more recent study investigated the effects of whole-plant extract preparations in patients with intractable cancer pain.[29] In all, 177 patients experiencing inadequate analgesia despite chronic opioid use were randomized to receive the THC:CBD extract ($N = 60$), the THC extract ($N = 58$), or placebo ($N =$

59) in a 2-week, multicenter, double-blind trial. Pain relief was superior in the THC:CBD group, with twice as many patients in the combination arm achieving a greater than 30% reduction in pain when compared to placebo. The THC alone group fared more or less the same as the placebo recipients. No change from baseline at a median dose of opioids or need for breakthrough medication was seen.

Neuropathy

Cannabinoids have also been shown to be of potential benefit in an animal model of neuropathic pain.[30] Neuropathic pain is a troubling symptom in cancer patients, especially those treated with platinum-based chemotherapy or taxanes. A painful sensory peripheral neuropathy is also commonly encountered in patients with HIV infection either as a consequence of HIV itself or antiretroviral drugs used in treatment of the infection. We completed a randomized, controlled trial of smoked cannabis compared to placebo in 50 subjects with HIV-related peripheral neuropathy.[31] Smoked cannabis reduced daily pain by 34% compared to 17% with placebo ($P = 0.03$). A greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($P = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% compared to 15% with placebo ($P < 0.001$). Cannabis also reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($P \leq 0.05$) in a heat-capsaicin experimental pain model used to anchor the more subjective response of the chronic neuropathic pain. No serious adverse events were reported. The NNT in this study was 3.6, which was virtually identical to the NNT in other studies of inhaled cannabis in HIV and other neuropathic syndromes.[32–34]

Two placebo-controlled studies of cannabinoids for central neuropathic pain associated with multiple sclerosis produced results similar to the aforementioned study. In a crossover trial of synthetic delta-9-THC up to 10 mg/day, a NNT of 3.5 was reported.[35] A trial of the sublingual spray containing delta-9-THC alone or combined with CBD showed a 41% pain reduction with active drug compared to a 22% reduction with placebo.[36] In this study, the CBD-alone preparation was ineffective in pain relief. Improvement in sleep quality was also reported with the sublingual spray. Nabiximols is currently approved in Canada for treatment of neuropathic pain related to multiple sclerosis as well as cancer-related pain. A small clinical trial has been conducted investigating nabiximols in 16 patients with chemotherapy-induced neuropathic pain, with results suggesting that larger follow-on clinical trials in this patient population are warranted.[37]

In an animal model of paclitaxel-induced neuropathic pain, chronic administration of the nonpsychoactive cannabinoid CBD prevented the onset of chemotherapy-induced neurotoxicity in mice.[38] The investigators suggested that adjunct treatment with CBD during taxane chemotherapy may be safe and effective in the prevention or attenuation of chemotherapy-induced neuropathic pain, although human studies are certainly required.

Cannabinoid:opioid interactions

Synergism between opioids and cannabinoids has been postulated and subsequently demonstrated in a number of animal models.[39] The antinociceptive effects of morphine are predominantly mediated by mu-opioid receptors but may be enhanced by delta-9-THC activation of kappa and delta-opioid receptors. It has been further postulated that the cannabinoid:opioid interaction may occur at the level of their signal transduction mechanisms. Receptors for both classes of drugs are coupled to similar intracellular signaling mechanisms that lead to a decrease in cAMP production by way of G_i protein activation. There has also been some evidence that cannabinoids might increase the synthesis or release of endogenous opioids, or both. With this background, we conducted a pharmacokinetic interaction study to investigate the effect of concomitant cannabis on disposition kinetics of opioid analgesics.[40] Ten patients with chronic pain on a stable dose of sustained-release morphine and 11 on sustained-release oxycodone had their opioid concentration over time curves evaluated before and after 4 days of exposure to vaporized cannabis. No adverse side effects of combining cannabinoids and opioids were observed over the course of the in-patient evaluation. There were no significant alterations in the area under the curves for the opioids after the addition of vaporized cannabis. Although the study was not powered for pain as an endpoint, evidence of potential synergistic relief of pain was appreciated. If cannabinoids and opioids were shown to be synergistic in a larger follow-on controlled clinical trial, it is possible that lower doses of opioids would be effective for longer periods of time with fewer side effects, clearly a benefit to the patient with pain.

Anxiety, depression, and sleep

In clinical trials of cannabis, euphoria is often scored as an adverse effect. Although not all patients experience mood elevation after exposure to cannabis, it is a frequent outcome. Much depends on the "set and setting" and the individual's prior experience with cannabis. Some people develop dysphoria with or without paranoia upon exposure to cannabis; for them, cannabis or its constituents may not be clinically useful. Sleepiness is another common side effect which can easily be recast as improved sleep quality, as has been reported in trials of nabiximols as well as inhaled cannabis.[41,42] For the cancer patient suffering from anorexia, nausea, pain, depression, anxiety, and insomnia, a single agent that can address all of these symptoms would be a valuable addition to the armamentarium. Cannabis may therefore be particularly useful in supportive or palliative care situations. [43]

CANNABINOIDS AS ANTICANCER AGENTS

There has been an increasing body of evidence over the past decade that cannabinoids may have a role in cancer therapy.[1,44–46] Evidence from cell culture systems as well as animal models has shown that THC and other cannabinoids may inhibit the growth of some tumors by the modulation of signaling pathways that lead to growth arrest and cell death as well as by inhibition of angiogenesis and metastasis. The antiproliferative effects were originally reported in 1975 by Munson *et al.*,[47] who demonstrated that delta-9-THC, delta-8-THC, and cannabinol inhibited Lewis lung adenocarcinoma cell growth *in vitro* as well as in mice. Curiously, there was no real follow-up of these findings for 20 years when the line of investigation was

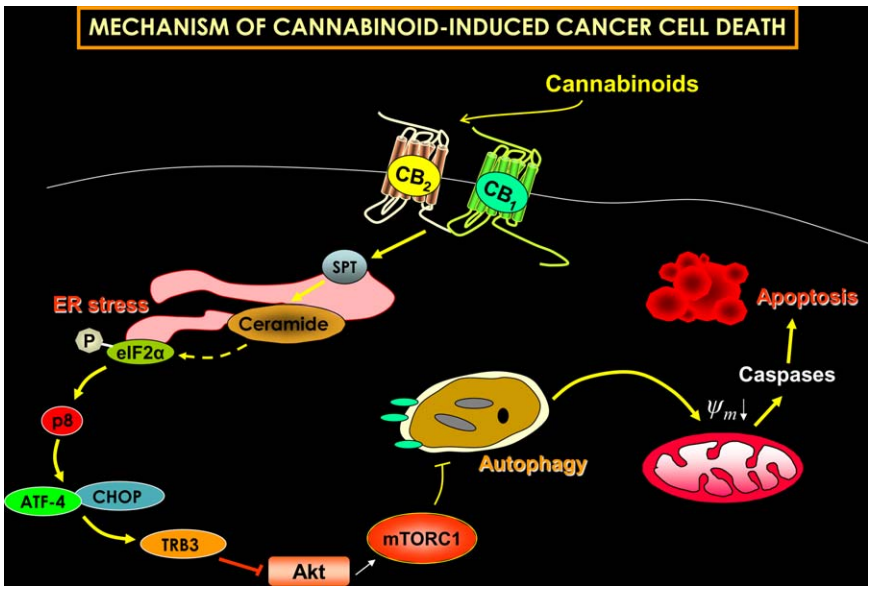

Figure 3 Mechanism of cannabinoid-induced cancer cell death. Cannabinoid agonists bind to CB_1 and/or CB_2 receptors to stimulate *de novo* synthesis of ceramide via induction of the enzyme serine palmitoyltransferase (SPT). This triggers the induction of an eIF2a-mediated endoplasmic reticulum (ER) stress response that promotes the up-regulation of the transcription factor p8 and several of its downstream targets, including the transcription factors ATF-4 and CHOP and the pseudokinase TRB3. This favors the interaction of TRB3 with the prosurvival protein AKT, thus leading to the inhibition of the AKT -mTORC1 axis and the subsequent induction of autophagy. Autophagy is upstream of intrinsic mitochondrial apoptosis in the process of cannabinoid-induced cell death.

picked up by scientists in Spain and Italy, who have remained at the forefront of this emerging field.[1,44–46,48] Since the late 1990s, several plant-derived (THC and CBD), synthetic (WIN-55,212-2 and HU-210), and endogenous cannabinoids (anandamide and 2-arachidonoylglycerol) have been shown to exert antiproliferative effects of a wide variety of tumor cells in culture systems. In addition to the original lung adenocarcinoma study, other tumor cells that have been shown to be sensitive to cannabinoid-induced growth inhibition include glioma, thyroid epithelioma, leukemia/lymphoma, neuroblastoma, and skin, uterus, breast, gastric, colorectal, pancreatic, and prostate carcinomas.[1,46,49–53] Perhaps even more compelling, cannabinoid administration to nude mice slows the growth of various tumor xenografts or genetically initiated tumors including lung, breast, colorectal, and skin carcinomas, thyroid epitheliomas, melanomas, pancreatic carcinomas, lymphomas, and gliomas. The requirement of CB1 and/or CB2 receptors for the antitumor effect has been shown by various biochemical and pharmacological approaches, and the cumulative effects of cannabinoid receptor signaling in the control of cell fate are expected to have important implications in the potential of cannabinoids for regulating tumor cell growth.

Cannabinoids may exert their antitumor effects by a number of different mechanisms, including direct induction of transformed cell death, direct inhibition of transformed-cell growth, and inhibition of tumor angiogenesis and metastasis (**Figure 3**). A desirable property of antitumor compounds is their preferential targeting of malignant cells. Cannabinoids appear to kill tumor cells but do not affect their nontransformed counterparts, and may even protect them from cell death. This is best exemplified by glial cells. Thus, cannabinoids have been shown to induce apoptosis of glioma cells in culture and regression of glioma cells in mice and rats by activating CB1 and CB2 receptors. In

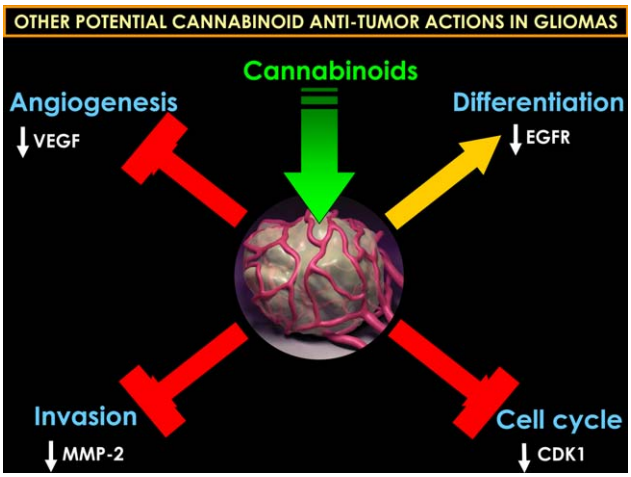

Figure 4 Other antitumor effects of cannabinoids. Besides inducing apoptosis of tumor cells, cannabinoid administration can decrease the growth of gliomas by other mechanisms, including at least: (i) reduction of tumor angiogenesis, by inhibition of the vascular endothelial growth factor (VEGF) pathway; (ii) inhibition of tumor cell invasion, by down-regulation of matrix metalloproteinase-2 (MMP-2) expression; (iii) induction of tumor cell differentiation, by down-regulation of epidermal growth factor (EGF) receptor expression; and perhaps (iv) arrest of the cell cycle, by down-regulation of cyclin-dependent kinase-1 (CDK1) expression. The relative contribution of these processes to the inhibition of tumor growth depends on various factors such as the type of tumor under study, the experimental model used and the intensity of cannabinoid signaling.

contrast, cannabinoids protect normal glial cells of astroglial and oligodendroglial lineages from apoptosis mediated by the CB1 receptor.

Immunohistochemical and functional analyses in mouse models of gliomas, skin carcinomas, and other tumors have demonstrated that cannabinoid administration alters the vascular hyperplasia characteristic of actively growing tumors into a pattern characterized by small, differentiated, impermeable capillaries, thus thwarting angiogenesis. This is accompanied by a reduced expression of vascular endothelial growth factor (VEGF) and other proangiogenic cytokines, as well as of VEGF receptors. Activation of cannabinoid receptors in vascular endothelial cells inhibits cell migration and survival, also contributing to impaired tumor vascularization. Cannabinoid administration to tumor-bearing mice decreases the activity and expression of matrix metalloproteinase 2, a proteolyic enzyme that allows tissue breakdown and remodeling during angiogenesis and metastasis. This supports the inhibitory effect of cannabinoids in inhibiting tumor invasion in animal models (**Figure 4**).

The use of combination anticancer therapies has a number of theoretical advantages over single-agent-based strategies as they allow the simultaneous targeting of tumor growth, progression, and/or spreading at different levels. In line with this idea, recent observations suggest that the combined administration of cannabinoids with other anticancer drugs acts synergistically to reduce tumor growth in mice. For example, the administration of THC and temozolomide (the benchmark agent for the management of glioblastoma) exerts a strong antitumor action in glioma xenografts, an effect that is also evident in temozolomide-resistant tumors.[54]

An additional approach has been to combine THC with CBD, a cannabinoid that reduces the growth of several types of tumor xenografts in mice through a still poorly defined mechanism. Combined administration of THC and CBD enhances the anticancer activity of THC and reduces the doses of THC needed to induce its tumor growth-inhibiting activity.[54,55] Moreover, the combination of THC and CBD together with temozolomide produces a striking reduction in the growth of glioma xenografts even when low doses of THC are used.[54] CBD is also known to alleviate some of the undesired effects of THC administration, such as seizures, incoordination, and psychotic events, and therefore improves the tolerability of cannabis-based medicines.[6] As *Cannabis sativa* contains an estimated 100 different cannabinoids, some of the other cannabinoids present in addition to CBD might also attenuate the psychoactive side effects of THC or even produce other therapeutic benefits. Thus, we believe that clinical studies aimed at analyzing the efficacy of cannabinoids as antitumor agents should be based not only on the use of both pure substances, such as THC and CBD, but also of cannabis products containing controlled amounts of THC, CBD, and other cannabinoids.

So with the body of evidence increasing, where are the clinical trials in humans with malignant disease? True, cannabinoids have psychoactive side effects, but these could be considered to be within the boundaries of tolerance for the toxicity profiles of cytotoxic chemotherapeutic and targeted small molecule therapies widely used in oncology. Ten years ago, a pilot clinical trial was carried out in collaboration between the Tenerife University Hospital and the Guzman laboratory in Madrid (Spain) to investigate the effect of local administration of THC intracranially through an infusion catheter on the growth of recurrent glioblastoma multiforme.[56] In this ground-breaking pilot study, THC administration was shown to be safe and associated with decreased tumor cell progression—as assessed by magnetic resonance imaging and biomarker expression criteria—in at least two of the nine patients studied. Two clinical studies aimed at evaluating the antitumoral activity of cannabinoids are currently ongoing (ClinicalTrials.gov Identifiers: NCT01812616 and NCT02255292).

Despite these impressive *in vitro* and animal model findings regarding the potential antitumor effects of cannabinoids, there is still no solid basis for ongoing claims by proponents of highly concentrated cannabis extracts or oils that these preparations can "cure cancer." Increasing numbers of patients in North America are seeking oils high in THC and/or CBD due to testimonials that patients have used these preparations either topically to eradicate skin cancers or systemically to eliminate nonskin cancers. This has led to a number of patients seeking to forego or postpone potentially curative conventional cancer therapies in favor of self-medicating with high-potency cannabis oils. Many patients claiming to be cured of their cancers have used the products in addition to conventional cancer therapies, thus obfuscating the issue further. Although the *in vitro* and animal evidence is intriguing, there have not yet been any robust human studies investigating cannabis as an anticancer agent that would warrant advising patients to forego conventional therapy in favor of using a high-potency cannabis extract. Patients who choose to delay conventional therapies in the hopes of benefiting from a trial of cannabis oil against their cancer risk the possibility of having a potentially treatable cancer become incurable. As the preclinical evidence suggests that cannabinoids might enhance the antitumor activity of conventional chemotherapeutic agents as well as ameliorate associated side effects, the addition of cannabinoid-based preparations to standard cancer therapy should not be discouraged by the treating oncologist.

CANNABIS AND CANCER RISK

A study conducted by the National Toxicology Program of the US Department of Health and Human Services on mice and rats suggested that cannabinoids may have a protective effect against tumor development.[57] In this 2-year evaluation, rats and mice were given increasing doses of THC by gavage. A dose-related decrease in the incidence of both benign and malignant tumors was observed. Animals receiving THC dosing also survived longer than those receiving vehicle alone.

The biology of mice and rats is certainly different from that of humans, and gavage is not equivalent to smoking a combusted botanical product. Many would find the combustion and inhalation of a therapeutic agent to be an undesirable and perhaps counterintuitive way to deliver a drug. Most of the evidence available on the risk of cancer from marijuana smoking comes from epidemiologic studies, naturally, as prospective, randomized

control trials are not possible. Over the years, reports of increased risks of lung cancer, oropharyngeal cancers, and prostate and cervical cancer have been most consistently reported. For each trial suggesting a possible increase in cancer incidence in chronic marijuana users, others have been published that appear to refute the association.

A 40-year cohort study of Swedish military conscripts evaluated for cannabis use in 1969–1970 found that in those who reported use of cannabis more than 50 times in their life, their risk of lung cancer in 2009 was increased 2-fold.[58] As tobacco use was nearly universal in this cohort, the association was present even after adjusting for tobacco use.

Another retrospective cohort study evaluated 64,855 Kaiser Permanente healthcare members seen between 1979 and 1985, and followed through 1993.[59] Men aged 15–49 were divided into four cohorts based on their use of tobacco and marijuana: never smoked either, smoked only cannabis, smoked only tobacco, smoked tobacco and cannabis. There were 5,600–8,200 men in each cell followed for an average of nearly 9 years. In the men who never smoked, there were two cases of lung cancer diagnosed over the follow-up period. In the men who smoked tobacco, either alone or in addition to marijuana, the risk of lung cancer was increased 10-fold. In the over 50,000 person-years of follow-up of men who only smoked marijuana, there were no documented cases of lung cancer; less than in the never smokers.

A population-based case–control study of the association between marijuana use and the risk of lung and upper aerodigestive tract cancers was performed in Los Angeles.[60] In all, 1,112 incident cancer cases (611 lung, 303 oral, 108 esophagus, 100 pharynx, 90 larynx) were matched to 1,040 cancer-free controls on age, gender, and neighborhood. A standardized questionnaire used during face-to-face interviews collected information on marijuana use expressed in joint-years, where 1 joint-year is the equivalent of smoking one marijuana cigarette per day for 1 year. The interviews also requested information on the use of other drugs including hashish, tobacco (all forms), and alcohol, sociodemographic factors, diet, occupational history, environmental factors including exposure to smoke, medical history, and family history of cancer. Data were presented as crude odds ratios and adjusted odds ratios using three models of covariate adjustment (with only Model 3 including tobacco use and pack/years). The results showed that although using marijuana for $\geq$30 joint-years was positively associated in the crude analysis with each cancer except pharyngeal, no positive associations were found when adjusting for several confounders including cigarette smoking. In fact, in the Model 3 analysis for lung cancer, the cohort who reported >0 to <1 joint-years of marijuana use had a 37% reduction in the risk of developing lung cancer compared to those who never smoked marijuana. Although this was the only cohort where the reduction in lung cancer risk reached statistical significance, in the model all levels of marijuana use (including $\geq$60 joint-years) had adjusted odds ratios (ORs) less than 1.0. The authors report adjusted ORs <1 for all cancers except oral cancer and found no consistent association of marijuana use with any malignant outcome. In what appears to be an overly aggressive attempt to delineate the possible limitations of their work that could have led to such a consistent yet startling result, the authors mention that "it is possible that marijuana use does not increase cancer risk.... Although the adjusted ORs < 1 may be chance findings, they were observed for all non-reference exposure categories with all outcomes except oral cancer. Although purely speculative, it is possible that such inverse associations may reflect a protective effect of marijuana."

A systematic review evaluating 19 studies that involved persons 18 years or older who smoked marijuana and examined premalignant or cancerous lung lesions concluded that observational studies failed to demonstrate significant associations between marijuana smoking and lung cancer after adjusting for tobacco use.[61] The authors site the selection bias, small sample size, limited generalizability, and overall young participant age in stating that because of the biological plausibility of an association of marijuana smoking and lung cancer, physicians should still caution patients regarding potential risks until further rigorous studies permit definitive conclusions. A more recent pooled analysis of six international case–control studies involving 2,159 lung cancer cases and 2,985 controls found weak associations between cannabis smoking and lung cancer in never tobacco smokers, but the authors suggested that the results provide little evidence of increased risk of lung cancer among habitual or long-term users while again cautioning that the possibility of adverse effect for heavy consumption cannot be excluded.[62]

Postulating that chronic use of cannabis impacts negatively on endocrine and reproductive systems, three recent investigations suggest an association between cannabis and testicular tumors.[63–65] These population-based case–control studies reported an association between marijuana use and elevated risk of especially nonseminomatous germ cell tumors. Although lacking good dose information and adequate sample sizes, the trends warrant further follow-up. A recent analysis from the California Men's Health Study reported that cannabis use may be inversely associated with bladder cancer risk in a study of 84,170 men aged 45–69.[66] A review of 34 epidemiologic studies acknowledges the possible association of cannabis use with testicular cancers, agrees that the data regarding lung cancer is confounded by concomitant tobacco use, and concludes that for other cancer sites the data are still insufficient to make any conclusions.[67] Finally, a comprehensive review from Health Canada concluded that although concerns exist, the epidemiologic evidence of a link between use of cannabis and cancer remains inconclusive (http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php).

SAFETY AND SIDE EFFECTS

Cannabinoids have an extremely favorable drug safety profile.[1,9,12,44] Unlike opioid receptors, cannabinoid receptors are not located in brainstem areas controlling respiration, so lethal overdoses due to respiratory suppression do not occur. The LD_{50} has been estimated to be 1,500 pounds smoked in 15 minutes as extrapolated from animal studies where the median lethal dose was estimated to be several grams per kilogram of body weight (http://www.fcda.org/pdf/young88.fcda.pdf).

The administration of cannabinoids to laboratory animals and humans does result in psychoactive effects. In humans, the central nervous system effects are both stimulating and depressing and are divided mainly into four groups: affective (euphoria and easy laughter); sensory (temporal and spatial perception alterations and disorientation); somatic (drowsiness, dizziness and motor incoordination); and cognitive (confusion, memory lapses and difficulty concentrating).

As cannabinoid receptors are not just located in the CNS but are present in tissues throughout the body, additional side effects of note include tachycardia and hypotension, conjunctival injection, bronchodilation, muscle relaxation, and decreased gastrointestinal motility. Tolerance to the unwanted side effects of cannabis appears to develop rapidly in laboratory animals and humans. This is felt to occur due to a decrease in the number of total and functionally coupled cannabinoid receptors on the cell surface, with a possible minor contribution from increased cannabinoid biotransformation and excretion with repeated exposure.

Although cannabinoids are considered by some to be addictive drugs, their addictive potential is considerably lower than other prescribed agents or substances of abuse. The brain develops tolerance to cannabinoids and animal research demonstrates a potential for dependence. Dependence is reported to develop in 9% of cannabis users according to the criteria in the *DSM-IV*.[68] The Institute of Medicine report puts this into context noting that, with 46% of the US population ever having used cannabis with 9% becoming dependent, the risk is much lower than that of nicotine, heroin, cocaine, and alcohol, and equivalent to the proportion of those dependent on anxiolytics.[9] Withdrawal symptoms—irritability, insomnia with sleep EEG disturbance, restlessness, hot flashes, and rarely nausea and cramping—have been observed, but are usually mild compared with the withdrawal from opiates or benzodiazepines and usually dissipate after a few days. Unlike other commonly used drugs, cannabinoids are stored in adipose tissue and excreted at a low rate (half-life 1–3 days), so even abrupt cessation of THC intake is not associated with rapid declines in plasma concentration that would precipitate withdrawal symptoms or drug craving.

The Institute of Medicine report addressed the frequent concern that marijuana is a "gateway drug" leading to use of other subsequent more potent and addictive substances of abuse.[9] The report recounts that marijuana is the most widely used illicit drug and, predictably, the first most people encounter. Not surprisingly, most users of other illicit drugs have used marijuana first. However, most drug users begin with alcohol and nicotine before marijuana; hence, marijuana would very rarely be the first "gateway" drug. The report summarizes that there is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs and cautions that data on drug use progression cannot be assumed to apply to the use of drugs for medical purposes, which is certainly pertinent to the discussion of cannabis in cancer patients.

GUIDELINES FOR PROVIDERS

The Institute of Medicine is aware that the development and acceptance of preferred smokeless marijuana delivery systems "may take years; in the meantime there are patients with debilitating symptoms for whom smoked marijuana may provide relief." So what is a provider to do? Patients with cancer have a number of symptoms that may be responsive to cannabinoid therapies. As enumerated, these include nausea, vomiting, anorexia, pain, insomnia, anxiety, and depression. Many providers would frown upon the use of a relatively benign inhaled psychotropic agent while freely writing prescriptions for pharmaceutical agents with significantly greater cost, potential for addiction or abuse, and more negative societal impact overall.

A Medical Board of California Action Report from 2004 provides a model for how states with medical marijuana legislation should advise physicians (http://www.caldocinfo.ca.gov). "The intent of the board at this time is to reassure physicians that if they use the same proper care in recommending medical marijuana to their patients as they would any other medication or treatment, their activity will be viewed by the Medical Board just as any other appropriate medical intervention."

The Board recommends following the accepted standards that would be used in recommending any medication. A history and physical examination should be documented. The provider should ascertain that medical marijuana use is not masking an acute or treatable progressive condition. A treatment plan should be formulated. A patient need not have failed all standard interventions before marijuana can be recommended. The physician may have little guidelines in actually recommending a concrete dose for the patient to use.[69] As there are so many variables associated with effect, the physician and patient should develop an individual self-titration dosing paradigm that allows the patient to achieve the maximum benefit with tolerable side effects. Discussion of potential side effects and obtaining verbal informed consent are desirable. Periodic review of the treatment efficacy should be documented. Consultation should be obtained when necessary. Proper record keeping that supports the decision to recommend the use of medical marijuana is advised.

The controlled medical use of cannabis preparations is currently legal in Austria, Canada, Czech Republic, Finland, Germany, Israel, Italy, the Netherlands, Portugal, and Spain. Although 23 states and the District of Columbia now have legislation allowing physicians to recommend medicinal cannabis to patients, it is still illegal on the federal level, causing many physicians to think twice before offering their patients this option. It is estimated that 70% of the US population lives in jurisdictions where they can access medical cannabis. Unfortunately, most physicians currently practicing medicine have been schooled during the prohibition era and have little or no knowledge of the biological actions of (endo)cannabinoids and the medicinal qualities of cannabis. Much of the discussion is dominated by addiction medicine specialists who have a skewed view of the health consequences of cannabis use by virtue of their specialty. Certainly a practicing oncologist is likely to have a much different perception of the risk:benefits of cannabis compared to the addiction medicine specialist (http://www.cancer.gov/cancertopics/pdq/cam/cannabis/healthprofessional/).

Recently, the *New England Journal of Medicine* presented the case of a 68-year-old woman with metastatic breast cancer seeking medicinal cannabis for symptom management.[70] Opposing arguments were presented. In all, 1,446 readers then participated in a poll, the results of which were reported in a subsequent article. The authors remarked "We were surprised by the outcome of polling and comments, with 76% of all votes in favor of the use of marijuana for medicinal purposes—even though marijuana use is illegal in most countries."[71] Hence, there is a suggestion that, with an increased and concerted educational effort aimed at healthcare providers, in the coming years medicinal cannabis may become an option for an even larger percentage of patients who may benefit from its use.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Using Medical Cannabis in an Oncology Practice

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My clinical experience as an oncologist practicing in San Francisco for 35 years is that cannabis is an effective antiemetic, even in situations where other pharmaceuticals have failed.

Introduction

As oncologists, we treat patients who have devastating diagnoses with potent therapies. Hence, we demand solid evidence before recommending any intervention. Unfortunately, when it comes to supporting the use of cannabis in clinical situations, we are frustrated by a dearth of convincing evidence. Data from gold-standard prospective randomized controlled clinical trials are virtually nonexistent. One reason for this is that the only legal source of cannabis for research in the United States is the National Institute on Drug Abuse (NIDA). NIDA has a congressional mandate to study substances of abuse *only* as substances of abuse and not as therapeutic interventions. Although NIDA can supply cannabis for clinical trials to assess its effectiveness, funding must come from elsewhere. However, in this era of gene therapy and nanotechnology, few investigators are interested in studying this ancient botanical medicine. In addition, just as cancer is many diseases, cannabis is many different strains, so standardization of cannabis medicine is a challenge.

How Has Medical Cannabis Been Utilized in Clinical Practice?

Delta-9-tetrahydrocannabinol (THC) is the most psychoactive of the 100 or so of the plant's 21-carbon–containing terpenophenolic compounds known as cannabinoids.[1] A number of other cannabinoids are thought to have medicinal benefit as well. Cannabidiol (CBD), for example, is believed to be analgesic and anti-inflammatory but is not psychoactive.[2] THC has been available as a licensed medicine in the United States since 1986, when dronabinol was approved for the treatment of chemotherapy-induced nausea and vomiting (CINV). The indication was expanded in 1992 to include treatment of anorexia associated with the AIDS wasting syndrome. Nabilone is another synthetic THC that became available in the United States in 2006 for the treatment of nausea and vomiting. Nabiximols is a whole plant extract delivered as an oromucosal spray that contains THC and CBD in a 1:1 ratio.[3-5] Nabiximols is approved in most of the European Union and Canada and continues to undergo clinical trials in the United States. Most of the available published research on the use of cannabis-based medicines involves these pharmaceutical agents, as studying the whole plant has been difficult, based on the reasons stated previously.

Dronabinol was approved 30 years ago for the treatment of CINV, and as such, it would stand to reason that the parent compound might also have activity for this indication. Again, most of the trial-generated data come from evaluation of the licensed pharmaceuticals and not the botanical itself. Only three trials have investigated cannabis, and in two of those trials the cannabis was only made available after dronabinol had failed.[6-8] Data from systematic reviews are generally more supportive of a benefit from cannabinoids.[9-12] My clinical experience as an oncologist practicing in San Francisco for 35 years is that cannabis is an effective antiemetic, even in situations where other pharmaceuticals have failed. Many patients choose cannabis over serotonin antagonists in hopes of avoiding the troublesome constipation often associated with those medications. Cannabis is also the only antiemetic that is an appetite stimulant. However, no clinical trials have been conducted to date evaluating the effect of the botanical therapy on cancer-related anorexia/cachexia syndrome. A trial of dronabinol found enhanced chemosensory perception of food in the treatment group compared with placebo, but larger studies with appetite and weight change endpoints were not impressive.[13] Nonetheless, patients employing cannabis in clinical practice often benefit from its orexigenic effect.

Our bodies have an intricate system of cannabinoid receptors and endogenous cannabinoids, known as endocannabinoids.[14] It has been postulated that the function of this system is to help us to process pain. Cannabis-based medicines have been tested in a number of pain models, and recent meta-analyses and systematic reviews suggest that they are beneficial in patients with chronic pain syndromes.[12,15,16] Patients with cancer pain as well as neuropathic pain from a number of causes have been included in these reviews. There is a con-

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vincing body of evidence showing cannabis itself is effective in a number of neuropathic pain syndromes, and cannabinoids seem to be able to treat, as well as prevent, chemotherapy-induced peripheral neuropathy caused by vinca alkaloids,[17] platinums,[18] and taxanes[19] in rodent models; however, only one small study of nabiximols has been published investigating this indication.[5] In the 16-patient placebo-controlled crossover trial, 5 responders reported a greater than 2-point decrease in their pain on a 0 to 10 numeric rating scale. Hence, further clinical trials of cannabis-based therapies in chemotherapy-induced peripheral neuropathy are warranted.

KEY POINTS

- The current dearth of convincing evidence supporting the use of cannabis in clinical situations is because it has been difficult to get access to the plant to study as a therapeutic intervention.
- Cannabis can be an effective anti-emetic and appetite stimulant and may also be beneficial for cancer patients with chronic pain and neuropathy.
- Internet testimonials about possible anti-cancer effects of cannabis have caused some patients to forego conventional cancer therapies; oncologists should emphasize that this is not a recommended course of action, especially in patients with a potentially curable malignancy.
- It is important that oncologists educate themselves about the use of medical cannabis, including mode of administration, appropriate strain, and potential side effects for patients with comorbidities.

> If I have a single medicine that I can recommend to assist with nausea, anorexia, insomnia, depression, and pain rather than prescribing five or six pharmaceuticals that may interact with each other or the patient's chemotherapy, I consider it an attractive option for my patients

In animal models, cannabinoids appear to be synergistic with opioids in producing analgesia. Based on these preclinical observations, we conducted a small pharmacokinetic interaction study.[20] Although we saw no effect on plasma concentration of morphine or oxycodone when adding vaporized cannabis to steady-state dosages of sustained-release preparations, we did appreciate synergistic pain relief, although the study was too small to make a definitive statement about a pain endpoint. That said, in my clinical practice I have seen many patients decrease their dose of narcotics or wean off them altogether with the addition of cannabis to their regimen. Pain relief, with or without opiates, is another area where cannabis may be quite useful. In a number of the published pain studies, medicinal cannabis has also been reported to be effective in improving sleep quality. Patients report that CBD-rich products may be particularly effective for insomnia.

Investigators at the National Cancer Institute first published results of in vitro and animal studies demonstrating the inhibitory effects of cannabinoids—delta-9-THC, delta-8-THC, and CBD—on cancer cell growth and proliferation.[21] This line of research subsequently moved to Spain and Italy, where an increasing body of preclinical evidence has been accumulating that confirms the early observations.[1,2,22-27] Internet testimonials abound from patients claiming to have cured their cancer by using highly concentrated oil extractions of cannabis, enriched for THC, CBD, or both. These reports have generated an interest in some patients to forego conventional cancer therapies and to treat their cancer with cannabis oil alone. This is a distressing situation, especially when faced with a patient with a potentially curable malignancy who chooses to go down this alternative pathway. As yet, there have been no clinical trials investigating highly concentrated cannabis products as anticancer agents, so patients must be reminded that what is observed in the test tube or animal models does not necessarily translate into benefit in humans.

Does Mode of Administration (Inhalation vs Oral Consumption) Matter?

When cannabis is inhaled, either as combusted or vaporized plant matter, the peak concentration of THC occurs in 2 to 5 minutes, with a rapid drop-off. The kinetics of inhaled oils, as one might find in the electric portable devices, may not yet be fully known. When ingested by mouth, the oral bioavailability is low and variable, estimated to be 5% to 20% of the ingested dose. In studies we conducted, the peak plasma concentration of THC taken by mouth was achieved at 2.5 hours and declined much more slowly. The terminal half-life of orally ingested THC is 25 to 30 hours, and when delta-9-THC passes through the liver it is metabolized into a psychoactive 11-hydroxy-THC, which may be even more psychoactive than the delta-9-THC. This is why people eating cannabis-baked products or capsules report a more significant psychoactive effect compared with those who inhale it (since in the second case, less of the secondary psychoactive metabolite is formed). A study investigating the pharmacokinetics of nabiximols delivered as

an oromucosal spray found values similar to those of orally administered THC.[28] The metabolism of sublingual highly concentrated extracts and oils currently being used by patients seeking an anticancer effect is not known at this time.

In view of these kinetics, I generally advise patients that if they want better control over the onset, depth, and duration of the effect, inhalation may be the better mode of delivery. However, I have heard from some patients who feel that while eating is a normal function, inhalation is not and may present additional health problems. As a result, they chose to go to a dispensary, where they were instructed to eat only a quarter of a cannabis cookie, but when the effects weren't felt right way, they ate the entire cookie. For a number of patients this created a degree of psychoactivity that was uncomfortable or frightening, sometimes necessitating medical evaluation and intervention. However, for sustained effects or overnight benefits, oral ingestion may be a more convenient mode of delivery than inhalation once proper dosing has been ascertained.

What Are the Obstacles to Obtaining Medical Cannabis?

Cannabis is now available for medical use in 23 states and the District of Columbia. California was the first state to approve medicinal cannabis in 1996. Over the past 2 decades, half of the states, accounting for 86% of the US population, have acquired access to cannabis as medicine. My patients in the San Francisco Bay Area have a wide assortment of dispensaries where they are able to obtain cannabis. It requires a letter from a physician (one hopes, the patient's own personal provider) recommending cannabis to the patient and stating that the physician will monitor the patient should he or she choose to use it. Alternatively, patients can pay a small fee and register with the state to obtain an identification card that allows them to access any dispensary.

Numerous barriers still exist. One is the patient's reluctance to try cannabis because of stigma that they associate with its use, or fear of addiction. I recall one 45-year-old patient with metastatic colon cancer receiving FOLFOX (leucovorin, fluorouracil, and oxaliplatin) who told me that it took him 5 cycles of his treatment to finally get over this stigma and try cannabis. He reported that it did what no other medicine could do—completely eliminate his CINV, and allow him to function quite normally. There are also physicians who have a persistent phobia about recommending cannabis, and often tell their patients that they receive federal funding and therefore cannot recommend cannabis; however, I find that odd as I have federal funding to do research on cannabis! There is currently a huge knowledge gap for physicians who may be interested in offering cannabis to their patients. Although cannabis has been used as a medicine for nearly 3,000 years, it was removed from the US Pharmacopeia in 1942. Hence, most of us have been trained during a time when cannabis was not an accepted medicine and, as a result, clinicians know very little about what it does and how to use it, nor do they understand what exactly is available for patients in the dispensaries. Even if physicians were aware of the strains and products available, in all likelihood they still would not be comfortable recommending one strain over another because of the total lack of evidence on which to base their decision (eg, whether CBD works for nausea, what the best ratio of THC:CBD is for sleep, or which oil is the most potent for pain relief).

How Can Oncologists Educate Themselves About Medical Cannabis?

Education is critical if we are going to be able to best advise our patients on how they might utilize cannabis, particularly for management of symptoms related to cancer or its treatment. Again, the dearth of evidence hinders our ability to feel confident in counseling patients. We simply do not know the answers to most of the questions our patients are asking about cannabis. I was recently interviewed by a think-tank person working with one of our local dispensaries to improve communications with physicians, who clearly outlined the problem. She remarked that when I see a patient with depression, I might write a prescription for paroxetine 20 mg once daily, bupropion 150 mg twice daily, or sertraline 50 mg once daily. The patient will take the prescription to the pharmacy, and will receive exactly what he or she needs. However, using an analogy to the way cannabis dispensaries work, a physician would write a recommendation for treating depression, and the dispensary would inquire, "do you want paroxetine, bupropion, or sertraline? What dose? How many?" An imperfect system for sure, but that is the way it currently works for medicinal cannabis.

Many things can influence how a person will respond to the use of cannabis medicines. Past experience, "set and setting," and even pharma-

SUGGESTED RESOURCES

Websites

International Association for Cannabinoid Medicines (IACM)
(www.cannabis-med.org)

International Cannabinoid Research Society
(www.icrs.co)

NCI PDQ CAM Cannabis and Cannabinoids
(www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq)

Patients Out of Time
(www.medicalcannabis.com)

Society of Cannabis Clinicians
(http://cannabisclinicians.org/)

The Canadian Consortium for the Investigation of Cannabinoids
(www.ccic.net)

University of California Center for Medicinal Cannabis Research
(www.cmcr.ucsd.edu)

Books

Backes M.
Cannabis Pharmacy: The Practical Guide to Medical Marijuana

Casarett D.
Stoned: A Doctor's Case for Medical Marijuana

Holland J.
The Pot Book: A Complete Guide to Cannabis - Its Role in Medicine, Politics, Science, and Culture

Pertwee RG.
Handbook of Cannabis

Werner C.
Marijuana Gateway to Health: How Cannabis Protects Us from Cancer and Alzheimer's Disease

cogenomics may all play a role. We recommend a self-titrated dosing regimen for the patient as the safest option, rather than attempting to prescribe an actual dose.[29] Aside from the psychoactivity of cannabis, which can be a dysphoric experience for some, side effects are generally tolerable. I am cautious about recommending cannabis to elderly patients, however, especially those with underlying heart disease, because cannabis can lower blood pressure and raise the heart rate. Postural hypotension and subsequent falls are also a concern. Colleagues who have studied cannabis in the preclinical setting describe euphoria as a side effect in their animal studies. I do not consider euphoria in my patients to be an adverse event by any means. If I have a single medicine that I can recommend to assist with nausea, anorexia, insomnia, depression, and pain rather than prescribing five or six pharmaceuticals that may interact with each other or the patient's chemotherapy, I consider it an attractive option for my patients. Hopefully, in the near future, more data will be generated from observational or interventional trials, which will allow us to feel even more confident recommending this ancient botanical to our patients.

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CURRENT ONCOLOGY

ORIGINAL ARTICLE

"J"

Integrating cannabis into clinical cancer care

D.I. Abrams MD*

ABSTRACT

Cannabis species have been used as medicine for thousands of years; only since the 1940s has the plant not been widely available for medical use. However, an increasing number of jurisdictions are making it possible for patients to obtain the botanical for medicinal use.

For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms. Cannabis is useful in combatting anorexia, chemotherapy-induced nausea and vomiting, pain, insomnia, and depression. Cannabis might be less potent than other available antiemetics, but for some patients, it is the only agent that works, and it is the only antiemetic that also increases appetite. Inhaled cannabis is more effective than placebo in ameliorating peripheral neuropathy in a number of conditions, and it could prove useful in chemotherapy-induced neuropathy. A pharmacokinetic interaction study of vaporized cannabis in patients with chronic pain on stable doses of sustained-release opioids demonstrated no clinically significant change in plasma opiates, while suggesting the possibility of synergistic analgesia.

Aside from symptom management, an increasing body of *in vitro* and animal-model studies supports a possible direct anticancer effect of cannabinoids by way of a number of different mechanisms involving apoptosis, angiogenesis, and inhibition of metastasis. Despite an absence of clinical trials, abundant anecdotal reports that describe patients having remarkable responses to cannabis as an anticancer agent, especially when taken as a high-potency orally ingested concentrate, are circulating. Human studies should be conducted to address critical questions related to the foregoing effects.

Key Words Cannabis, cannabinoids, symptom management, nausea, anorexia, pain

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INTRODUCTION

Much attention has been paid to the unearthing of the 2500-year-old mummy known as the "Siberian Ice Maiden." Discovered in 1993, her subterranean burial chamber included a pouch of cannabis among other archeologic findings[1]. Magnetic resonance imaging revealed that the princess had a primary tumour in the right breast, with axial adenopathy and metastatic disease. It is hypothesized that the cannabis was used to manage her pain and perhaps other symptoms, or even possibly as a treatment for her malignant disease.

Widely used as medicine during the ensuing millennia, cannabis disappeared from the pharmaceutical armamentarium in the 1940s as its prohibition took hold. Today, we are in the midst of what appears to be something of a medicinal cannabis renaissance, with patients across the globe gaining increased access to this potent botanical medicine. In a 2014 WebMD poll, 82% of oncologists indicated their belief that patients should have access to cannabis, ranking highest among medical subspecialists in their support[2]. Regrettably, most oncologists trained during the era of cannabis prohibition and have no knowledge of how to use the plant as medicine. In these days of targeted therapies and nanotechnology, the modern oncologist might feel somewhat ill at ease recommending a herbal intervention, notwithstanding the number of potent cytotoxic chemotherapeutic agents derived from plants.

An even more vexing concern to the oncologist is the lack of data on which to base treatment recommendations. Given the nature of the drugs that they prescribe, oncologists are used to seeing strong evidence of a favourable risk–benefit ratio before recommending a therapeutic intervention. Usually, oncology drugs have proceeded through preclinical studies, followed by the traditional phase I, II, and III analyses, before we feel comfortable adding them to our toolbox. Such data about the clinical effectiveness of medicinal cannabis are all but lacking.

In the United States, cannabis is classified as a Schedule I agent with a high potential for abuse and no accepted medical use. The study of cannabis requires a special Schedule I license from the U.S. Drug Enforcement

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Administration. In addition, the only legal source of cannabis for clinical trials is the National Institute on Drug Abuse, which has a congressional mandate to study substances of abuse only as substances of abuse. Although investigators can obtain National Institute on Drug Abuse cannabis to conduct effectiveness clinical trials, funding must come from another source. Hence, carefully controlled clinical trials of cannabis as a therapeutic agent—the sorts of trials that would satisfy a data-driven oncologist—are quite rare.

In 1986, Δ^9-tetrahydrocannabinol (THC), the most psychoactive cannabinoid in the plant, was approved as a licensed drug, dronabinol (Marinol: AbbVie, North Chicago, IL, U.S.A.), for the treatment of chemotherapy-induced nausea and vomiting. Hence, oncologists probably have the longest record of using a cannabis-based medicine. In 1992, the dronabinol indication was expanded to include treatment of the anorexia associated with AIDS wasting syndrome. In 2006, nabilone (Cesamet: Meda Pharmaceuticals, Somerset, NJ, U.S.A.) another synthetic THC that had long been available in Europe and elsewhere became available in the United States as well.

The foregoing drugs are THC alone and do not include any of the other potentially therapeutic cannabinoids, terpenoids, or flavonoids that are present in the whole plant[3]. Cannabidiol (CBD), in particular, is another of the phytocannabinoids that has been generating significant interest for its potential therapeutic effects[4]. Nabiximols (Sativex: GW Pharmaceuticals, Salisbury, U.K.) is a whole-plant extract of cannabis that has been processed to have a THC:CBD ratio of 1:1. Originally approved in Europe for the treatment of central pain associated with multiple sclerosis, this sublingual preparation has also been studied in a number of cancer-related conditions[5–8]. Because most of the information derived from clinical trials on cannabinoids in cancer is derived from studies of those licensed pharmaceuticals, the present review discusses findings from studies of those agents as well as from studies of cannabis itself.

CANNABIS FOR PAIN

To date, two types of cannabinoid receptors (seven-transmembrane domain G protein–coupled receptors) have been identified in humans and other animal species[9]. The CB1 receptor, initially identified in the brain, is found in high concentrations in areas involved in the processing of noxious stimuli. The CB2 receptor is predominantly located in cells of the immune system and likely has a role in the control of inflammation and cell proliferation.

The CB receptors are not present to react with the phytocannabinoids from cannabis alone. They exist because, on demand, humans produce endogenous cannabinoids—"endocannabinoids"—that react with the receptors, effecting changes in intracellular signalling. It has been suggested that the entire function of the system of cannabinoid receptors and endocannabinoids might be to assist in modulation of the response to pain. With that in mind, it is not surprising that an increasing body of knowledge is being developed about the effects on pain of cannabinoid medicines.

A recently published systematic review[10] considered 28 studies involving a total of 2454 participants and preparations including inhaled cannabis, dronabinol, nabilone, and nabiximols, among others. Twelve of the studies investigated neuropathic pain, and three looked at patients with cancer pain. The studies generally showed improvement in pain measures, with an overall odds ratio of 1.41 (95% confidence interval: 0.99 to 2.00) for improvement in pain with the use of cannabinoids compared with placebo. An earlier systematic review of eighteen randomized controlled trials of cannabinoids in 766 participants with chronic non-cancer pain found that fifteen of the studies reported a significant analgesic effect for the cannabinoids compared with placebo, and a number of the studies also noted improvements in sleep[11]. Another review that included six of those eighteen studies in patients with cancer-related pain also favoured cannabinoids[12].

Neuropathic pain is certainly problematic in cancer patients[13]. A systematic review of six randomized, double-blind, placebo-controlled trials of cannabinoids (five specifically addressing neuropathic pain) found evidence for the use of low-dose medical cannabis in refractory neuropathic pain in conjunction with traditional analgesics[14]. Another analysis reviewed five trials of inhaled cannabis in patients with HIV-related peripheral neuropathy and again found a positive effect for cannabis compared with placebo[15]. A recent small study[16] showed a dose–response effect for vaporized cannabis in the relief of pain from diabetic peripheral neuropathy, a huge clinical problem estimated to affect 238 million people worldwide.

With all of those impressive data suggesting that cannabinoids could be effective in peripheral neuropathy, where are the studies in patients with chemotherapy-induced peripheral neuropathy? Preclinical studies in rodent models have suggested that cannabinoids might actually be able to prevent peripheral neuropathy. Activation of the CB1 and CB2 receptors suppresses the development of vincristine-induced peripheral neuropathy in rats[17]. In mice receiving daily cisplatin, administration of anandamide (an endocannabinoid) together with an inhibitor of the fatty-acid amide hydrolase that metabolizes anandamide attenuated chemotherapy-induced peripheral neuropathy[18]. Cannabidiol pretreatment stops paclitaxel-induced neuropathy in mice[19]. To date, the only human study of a cannabis-based medicine in chemotherapy-induced peripheral neuropathy is a crossover placebo-controlled trial of nabiximols[20]. Overall, reported pain scores were not different with nabiximols and with placebo. However, on a 0–10 scale, 5 responders reported a greater than 2-point decline in neuropathic pain. That observation suggests that 5 patients have to be treated with the sublingual preparation for 1 to experience clinical benefit (an acceptable number-needed-to-treat for a neuropathic condition), suggesting that further investigation of cannabis medicines in chemotherapy-induced peripheral neuropathy is warranted. Even more exciting would be a study demonstrating the potential for cannabis to actually lower the risk for neuropathy or to prevent it from developing in the first place, as the animal models suggest.

In animal models, cannabinoids and opioids have been demonstrated to have synergistic analgesic effects[21].

Analgesic effects of cannabinoids are not blocked by opioid antagonists, suggesting that the two types of agents work through different receptors and pathways. An early study found that THC was ineffective as an analgesic on its own, but that it slightly increased the effect of morphine on 2 of 3 measures[22]. A randomized controlled trial of dronabinol in patients on opioids for chronic pain found that, compared with placebo, dronabinol reduced pain ($p < 0.01$) and increased patient satisfaction ($p < 0.05$)[23]. A randomized controlled trial of nabiximols in 359 cancer patients with poorly controlled pain despite a stable opioid regimen found that the sublingual preparation (4, 10, or 16 sprays daily for 5 weeks) reduced both pain and sleep disruption[24]. A pharmacokinetic interaction study of vaporized cannabis in 21 patients with chronic—mostly non-cancer—pain taking sustained-release morphine or sustained-release oxycodone showed no significant effect on plasma levels of the opiates, but a suggestion of enhanced analgesia[25]. However, that small study was not powered for a pain endpoint, suggesting that a larger follow-on trial is warranted[26].

Clinically, I have observed that many cancer patients benefit from adding cannabis to their pain regimen. Although the effect on chemotherapy-induced peripheral neuropathy has not been glaringly obvious, other sorts of cancer-related pain appear to respond. Patients who have been put on high doses of opiates at the end of life by their well-meaning oncologist or palliative care team frequently feel totally unable to communicate with their loved ones in their precious remaining time because of altered cognition. Many have successfully weaned themselves down or off their opiate dose by adding cannabis to their regimen. Although it would seem that THC-dominant strains of cannabis would be most likely to have analgesic effects, patients often report significant pain reduction from strains that are predominantly CBD-rich. Although CBD does not actually bind to the CB1 receptor, it does block the fatty-acid binding protein that transports the endocannabinoid intracellularly to be hydrolyzed by the fatty-acid amide hydrolase, hence allowing the endogenous cannabinoid complexed with the receptors to persist[27].

CANNABIS FOR NAUSEA

As an oncologist practicing medicine in San Francisco since the early 1980s, I have often said that I need a clinical trial to demonstrate that cannabis is an effective antiemetic about as much as I need a placebo-controlled trial to demonstrate that penicillin is an antibiotic! It would appear that, if the single most active constituent of the plant is licensed and approved for treatment of chemotherapy-induced nausea, that the parent botanical should also work. Being aware that the plural of anecdote is not evidence, I would like to share an e-mail message from a 42-year-old gentleman with metastatic colon cancer requesting a renewal of his medical cannabis authorization:

> *Although I did not use it until my last 5 sessions of chemo (me getting over the stigma of its use), it did what no other drug could do, completely solve the severe nausea I had.*
>
> *It allowed me to play with my children, attend their sports and school functions, and just function very normally in day to day activities.*
>
> *I cannot thank you enough for giving me that option!*
>
> *I am currently on a chemo vacation after a clean scan, and the only time I use medical marijuana now is when I have trouble sleeping. I would like to continue to use it for that purpose instead of relying on pharmaceutical options like zolpidem etc.*

That message is representative of what many patients have recounted to me over the past 30-plus years of oncology practice in a locale in which patients have never had difficulty accessing cannabis. However, data from controlled clinical trials of cannabis are less impressive.

Only three trials have looked at cannabis in the treatment of chemotherapy-induced nausea and vomiting, and in two of them, cannabis was made available only after dronabinol had already failed. The first trial noted a significant benefit for cannabis compared with placebo in patients receiving high-dose methotrexate[28]. A later study by the same investigators made cannabis available to patients receiving cyclophosphamide or doxorubicin after dronabinol failure, and no beneficial effect was noted[29]. The third study investigating cannabis was a randomized crossover trial in 20 patients who received dronabinol and cannabis[30]. Overall, 5 of the patients reported a positive antiemetic response. Of the entire cohort, 4 patients preferred smoked cannabis, 7 preferred dronabinol, and 9 had no preference. A recent phase II investigation in 16 patients of nabiximols, the sublingually delivered whole-plant extract, found that 4.8 sprays daily was more effective than placebo in conjunction with standard antiemetics[31].

Data from studies investigating the synthetically available versions of Δ^9-THC have provided more convincing evidence. A quantitative systematic review[32] that included 30 randomized comparisons of oral nabilone, oral dronabinol, or the intramuscular levonantradol preparation (no longer available) with placebo in 1366 patients receiving chemotherapy found that, as antiemetics, cannabinoids were more effective than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride (risk ratio: 1.38; 95% confidence interval: 1.18 to 1.51). For complete control of nausea, the number needed to treat was 6, and it was 8 for complete control of vomiting. In crossover trials, the patients preferred cannabinoids for future chemotherapy cycles. A later systematic review[33] of thirty randomized controlled trials involving 1138 patients also found that cannabinoids were more effective than placebo or conventional antiemetics in reducing chemotherapy-induced nausea and vomiting, and that patients preferred the cannabinoids. Adverse effects were noted to be more intense and to occur more frequently in patients using cannabinoids. A more recent systematic review[10] of twenty-eight randomized controlled trials (twenty-three using nabilone or dronabinol) involving 1772 participants reported an overall benefit for cannabis. A Cochrane review[34] analyzed twenty-three randomized controlled trials of cannabinoids compared with placebo

or with other antiemetic drugs. Patients were more likely to report a complete absence of nausea and vomiting with cannabis than with placebo, and there was little discernable difference between the effectiveness of cannabinoids and of prochlorperazine, metoclopramide, domperidone, and chlorpromazine. Notably, however, none of the trials involved the agents now most widely used—the serotonin 5-HT_3 antagonists. The National Comprehensive Cancer Network guidelines cautiously mention cannabinoids as a breakthrough treatment for chemotherapy-induced nausea and vomiting not responsive to other antiemetics[35].

CANNABIS FOR APPETITE STIMULATION

Although cannabis is the only antiemetic that is also orexigenic, no clinical trials investigating the plant as a treatment for cancer-related anorexia–cachexia syndrome have been conducted to date. A randomized placebo-controlled clinical trial evaluating a cannabis extract and dronabinol in 243 patients with cancer-related anorexia–cachexia syndrome found that neither preparation was superior to placebo with respect to affecting appetite or quality of life[36]. A large study of 469 advanced cancer patients randomized participants to receive the progestational agent megestrol acetate or dronabinol, or both[37]. Compared with participants in the dronabinol group, those in the megestrol arm experienced a significantly greater increase in both weight and appetite, and combining dronabinol with megestrol offered no additional benefit compared with megestrol alone. One smaller study of dronabinol in cancer patients demonstrated enhanced chemosensory perception in the treatment group compared with the placebo group[38]. In the dronabinol recipients, food tasted better, and appetite and caloric intake increased. Similarly variable and largely unimpressive results for dronabinol with respect to appetite and weight in HIV-associated wasting have also been reported[39].

CANNABIS FOR CANCER

One of the lay accounts concerning the tomb of the Siberian Ice Maiden closes with these lines:

> *Modern-day scientists have increasingly been turning their attention to cannabis due to its potential to inhibit or destroy cancer cells, and at the very least, manage the pain and symptoms that come with the illness. But then, ancient people seem to have known that already.*[40]

That sort of a leap—assuming that because the Ice Maiden was buried with cannabis and had cancer, that she was using it to treat her cancer—is about as valid as the claims being made on the Internet today that highly concentrated cannabis oils can cure cancer. It might be possible, but there is, as yet, no solid evidence to support that belief. One of the more distressing situations that oncologists increasingly face is trying to counsel the patient who has a curable diagnosis, but who seeks to forego conventional cancer treatment in favour of depending on cannabis oil to eradicate their malignancy because of the large number of online testimonials from people claiming such results. Given my long practice in San Francisco, I can assume that a large proportion of my patients have used cannabis during their journey. If cannabis cured cancer, I would have a lot more survivors in my practice today. Granted, inhaled cannabis cannot deliver the concentration of active ingredients that a heavily concentrated THC or CBD oil can, but there is as yet no convincing demonstration that the *in vitro* or animal model findings translate into the clinical arena.

One of the earliest studies suggesting that cannabinoids might have anticancer activity came from the U.S. National Cancer Institute in a paper published in 1975[41]. Investigators reported that Δ^9-THC, Δ^8-THC, and CBD inhibited the growth of Lewis lung adenocarcinoma cells *in vitro* and in mice. For unclear reasons, that line of research was not pursued further at the National Institutes of Health in the United States, but was subsequently picked up by investigators in Spain and Italy, who have made enormous contributions to the field.

If cannabinoids are postulated to have a potential anticancer effect working through the CB1 receptor, it would follow that the brain—where the CB1 receptor is the most densely populated seven-transmembrane domain G protein–coupled receptor—would be a good place to start the investigation. And, in fact, numerous studies *in vitro* and in animal models have suggested that cannabinoids can inhibit gliomas[42]. Other tumour cell lines are also inhibited by cannabinoids *in vitro,* and cannabinoid administration to nude mice curbs the growth of various tumour xenografts representing multiple solid and hematologic malignancies, including adenocarcinomas of the lung, breast, colon, and pancreas, and also myeloma, lymphoma, and melanoma[43,44].

A discussion of the mechanism of action of cannabinoids as anticancer agents is beyond the scope of the present article, but has been reviewed elsewhere[45–48]. Cannabinoids appear to induce apoptosis, probably through interaction with the CB1 receptor. Cannabinoid administration in mouse models has been observed to reduce the expression of vascular endothelial growth factor and its receptors, leading to inhibition of angiogenesis. Cannabinoids also decrease the activity of matrix metalloproteinase 2, leading to decreased tumour-cell invasiveness and decreased potential for metastasis. In addition, cannabinoids have anti-inflammatory and antioxidant properties that are also desirable in combatting cancer. *In vitro* studies have demonstrated that, combined with gemcitabine, cannabinoids further reduce the viability of pancreatic cancer cells[49]. In mice, adding THC to temozolomide (used widely in treatment of aggressive brain tumours), reinstated glioma suppression in tumours that had become resistant to chemotherapy[50]. The addition of CBD enhanced the antitumour activity even when lower doses of THC were used. Similarly, a combination of THC and CBD was found to enhance the antitumour effects of radiation in a murine glioma model, suggesting that cannabinoids might be synergistic with radiation therapy as well as with chemotherapy[51].

But again, mice and rats are not people, and what is observed *in vitro* does not necessarily translate into clinical medicine. The preclinical evidence that cannabinoids

might have direct anticancer activity is provocative as well, but more research is warranted. Hence, the oncologist advising patients on the use of cannabinoids during conventional cancer treatment should be aware of the preclinical findings and should not reflexively advise patients to avoid cannabis altogether. Currently, we can be confident that cannabis could have utility in symptom management for patients living with and beyond cancer[52–54]. Compared with most of the therapeutic agents that oncologists use in their practice, the side-effect profile of cannabis as medicine is acceptable, and the adverse effects are well described[54,55]. To be able to suggest a single agent that could hold benefit in the treatment of nausea, anorexia, pain, insomnia, and anxiety instead of writing prescriptions for 5 or 6 medications that might interact with each other or with cancer-directed therapies seems advantageous. And although botanical–pharmaceutical interactions for other drugs metabolized by certain cytochrome P450 isoforms is a theoretical possibility, no significant perturbations in the plasma concentrations of prescription medications have been seen to date when cannabis is co-administered. The only published study investigating medicinal cannabis with chemotherapeutic agents found no effect on the plasma pharmacokinetics of irinotecan or docetaxel when cannabis was administered as a herbal tea, although that delivery system is neither particularly popular nor likely potent[56]. The pharmacokinetics of ingested compared with inhaled cannabis would support an inhaled route of administration if patients desire more control over the onset, depth, and duration of the effect.

CONCLUSIONS

The august *New England Journal of Medicine* published a perspective piece describing Marilyn, a 68-year-old woman with metastatic breast cancer seeking medical cannabis from her physician[57]. Interestingly, the pro and con sides of the argument were both presented by mental health practitioners and not by medical oncologists. In a follow-up blog poll, the authors reported finding it surprising that 76% of the 1446 physicians responding from around the world were in favour of medicinal cannabis, even though many came from jurisdictions in which it is totally illegal[58]. The authors of a later WebMD survey of 1566 physicians in the United States reported that 82% of oncologists and hematologists were in favour of patients having access to medical cannabis—representing the strongest approval among all medical subspecialties[2].

To summarize, cannabis and cannabinoids are useful in managing symptoms related to cancer and its treatment. Exciting preclinical evidence suggests that cannabinoids are not only effective in the treatment but also in the prevention of chemotherapy-induced peripheral neuropathy. Cannabinoids could be synergistic with opioids in the relief of pain. The safety profile of cannabis is acceptable, with side effects that are generally tolerable and short-lived. Preclinical data suggest that cannabinoids could have direct antitumour activity, possibly most impressive in central nervous system malignancies. Clinical data about the effects of cannabis concentrates on cancer are as yet unavailable. Oncologists could find cannabis and cannabinoids to be effective tools in their care of patients living with and beyond cancer.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare the following interests: I have received fees as an advisory board member for ABcann Medicinals, MMJ PhytoTech, Tikun Olam, and Zynerba Pharmaceuticals.

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Critical Review

Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data

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Abstract: **Chronic neuropathic pain, the most frequent condition affecting the peripheral nervous system, remains underdiagnosed and difficult to treat. Inhaled cannabis may alleviate chronic neuropathic pain. Our objective was to synthesize the evidence on the use of inhaled cannabis for chronic neuropathic pain. We performed a systematic review and a meta-analysis of individual patient data. We registered our protocol with PROSPERO CRD42011001182. We searched in Cochrane Central, PubMed, EMBASE, and AMED. We considered all randomized controlled trials investigating chronic painful neuropathy and comparing inhaled cannabis with placebo. We pooled treatment effects following a hierarchical random-effects Bayesian responder model for the population-averaged subject-specific effect. Our evidence synthesis of individual patient data from 178 participants with 405 observed responses in 5 randomized controlled trials following patients for days to weeks provides evidence that inhaled cannabis results in short-term reductions in chronic neuropathic pain for 1 in every 5 to 6 patients treated (number needed to treat = 5.6 with a Bayesian 95% credible interval ranging between 3.4 and 14). Our inferences were insensitive to model assumptions, priors, and parameter choices. We caution that the small number of studies and participants, the short follow-up, shortcomings in allocation concealment, and considerable attrition limit the conclusions that can be drawn from the review. The Bayes factor is 332, corresponding to a posterior probability of effect of 99.7%.**

Perspective: ***This novel Bayesian meta-analysis of individual patient data from 5 randomized trials suggests that inhaled cannabis may provide short-term relief for 1 in 5 to 6 patients with neuropathic pain. Pragmatic trials are needed to evaluate the long-term benefits and risks of this treatment.***

Key words: *Cannabis, chronic pain, neuropathy, painful, polyneuropathy, meta-analysis, meta-analysis of individual patient data, Bayesian analysis, human immunodeficiency virus.*

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Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.

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About 1 in 40 adults in the general population has chronic neuropathic pain, making it the most frequent condition affecting the peripheral nervous system.[52] Chronic neuropathic pain presents a heterogeneous burden with a large prevalence[12] in certain susceptible subpopulations, for example in people living with human immunodeficiency virus (HIV).[30] HIV-related distal sensory neuropathy affects every third patient.[30] Chronic neuropathic pain may result from diverse insults, including diabetes, HIV, trauma, and certain medications.[86,87] Chronic neuropathic pain remains underdiagnosed and difficult to treat.[33] Regardless of the cause, chronic neuropathic pain persists despite attempts at management with opioids, nonsteroidal anti-inflammatory drugs, anticonvulsants (gabapentin), anti-inflammatory agents, antidepressants, and complementary medicines.[33]

A recent systematic review concluded that cannabis is effective in selected neurological disorders, including multiple sclerosis, but did not address chronic neuropathic pain.[50] Considering the recent wave of cannabis legalization,[76] continued legal wrangling,[65] its widespread medicinal and recreational use,[80,88] and additional randomized controlled trials (RCTs) published on cannabis recently, we performed a meta-analysis to investigate if inhaled cannabis alleviates chronic neuropathic pain.[8,81,84] Previous (systematic) reviews did not investigate inhaled cannabis for chronic neuropathic pain or were unable to synthesize all available data, did not include recently published RCTs, and varied considerably in their inclusion criteria, study selection, and data synthesis, leading to conflicting and outdated conclusions.[13,19,23,47,50,54-56,63,67,76,79,89] As cannabis should undergo the same evidence-based review[39] as other potent prescription medications,[83] an update is needed.[81,84]

In cooperation with all primary study authors, we performed an individual patient data Bayesian[35] meta-analysis of RCTs[71] (Supplementary Box 1). Although classic meta-analysis pools aggregate data extracted from published study reports, meta-analysis of individual patient data synthesizes the original data of the individual participants obtained from the primary study authors.[75] This often gives meta-analysis of individual patient data more power.[75] We selected Bayesian evidence synthesis for the analysis, anticipating that incomplete outcome reporting, varied endpoints, limited availability of aggregate or individual patient data, and diversity of study designs with varied statistical analysis approaches would pose a formidable challenge to the classic (frequentist) methods of meta-analysis.[74] Classic meta-analysis may also underestimate the between-study variability for small numbers of trials,[24,73] leading to inaccurate inferences; Bayesian methods provide more robust estimates of between-study variance.

Objectives

We performed a Bayesian responder meta-analysis of individual patient data to study whether inhaled cannabis provides relief for chronic neuropathic pain.

Methods

We registered our protocol with PROSPERO.[5] We identified studies by a combination of electronic and manual searches (Fig 1) (Supplementary Appendix 1). We followed the recommendations of the QUORUM and PRISMA statements,[59] including the PRISMA checklist (Supplementary Appendix 2). We searched in Cochrane Central, PubMed, EMBASE, and AMED without any language restriction with a combination of free text and controlled vocabulary, using the highly sensitive search strategy.[44] We conducted a hand search in the conference abstracts from the Conference on Retroviruses and Opportunistic Infections 2011, the International AIDS Conference, and the World Congress of Pain 2010 and reference lists.

We considered RCTs investigating chronic painful neuropathy. We included diabetic, traumatic, and HIV-related causes. We excluded multiple sclerosis, a central rather than a peripheral pain condition. The nature of the intervention likely interfered with effective participant blinding,[3] which was therefore not required for study inclusion. We only included studies comparing inhaled *Cannabis sativa* with placebo, because inhaled whole-herb cannabis differs significantly in composition, bioavailability, and pharmacodynamics from synthetic cannabinoids.[70]

Three review authors (M.H.A., G.C., K.S.) screened the citations using explicit criteria for study exclusion. Using a standard data collection form, 2 authors (M.H.A. and G.C.) extracted the data independently, reconciling any differences by consensus. Study authors provided individual patient data.[2,31,81,84,85] We recorded details of trial design, conflict of interests, sponsors, participant

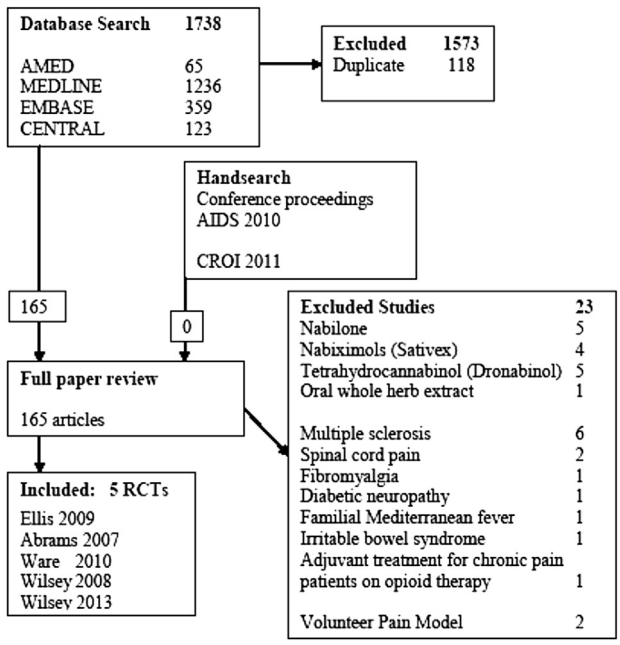

Figure 1. The QUORUM flow chart details our search in a diagram. We selected 165 articles for full review from 1738 hits in multiple electronic databases; 5 RCTs met the inclusion criteria (Abrams 2007,[2] Ellis 2009,[31] Ware 2010,[81] Wilsey 2008,[85] Wilsey 2013[84]). Excluded studies are double counted if they met more than 1 exclusion criterion, eg disease and mode of administration.

characteristics, interventions and outcome measures, inclusion and exclusion criteria, comorbidity and HIV status, cannabis provenance, dose, and mode of administration. We extracted data on attrition and on adverse effects.

We compared the proportion of patients experiencing more than 30% clinical improvement in chronic neuropathic pain assessed with a continuous patient-reported instrument (eg, the visual analog scale) at baseline and after treatment with inhaled cannabis. In essence, we dichotomized the outcome in a responder analysis, emerging as the preferred method for pain outcomes research.[28,32] We chose this patient-centered concept of minimally clinically important difference,[58] because chronic neuropathic pain, our primary outcome, is patient reported and may have a skewed distribution, with no more than 40 to 60% of patients obtaining even partial relief of their pain.[27] A statistically significant change in the population mean of a continuous pain outcome may not correspond to a clinically meaningful improvement for many individual patients.[60] In other words, large studies may detect population differences too small for individual patients to appreciate. However, responder analysis converts continuous pain outcomes to dichotomous responder data allowing a more meaningful comparison between interventions.[61,72] By convention, we classified participants as "responders" if their reduction in continuous spontaneous pain outcome (eg, VAS score) was larger than 30% after treatment.[28,32]

Two authors (G.C. and M.H.A.) independently assessed the risk of bias of the studies included according to the Cochrane Collaboration[44] on the basis of a checklist of design components and they contacted authors for missing information. We summarized this in a risk of bias graph (Fig 2) and provide detailed information in Supplementary Table 1. This comprised randomization, allocation concealment, observer blinding, intention-to-treat analysis, selective reporting, and conflict of interests. We achieved consensus by informal discussion. With inhaled cannabis interventions, blinding of patients and providers can be difficult and hence they received less weight in the evaluation of performance bias but not with regard to detection bias.

Our results are based on individual patient data obtained from primary authors who helped resolve data inconsistencies when evident. We estimated the content and the dose administered following published methods[10,57] in cooperation with the primary study authors.

We compared the reported primary outcome with the planned primary outcome in the study protocols to assess reporting bias. We explored undue sponsor influence.[44] We considered an examination of publication bias using graphical and statistical tests.[29] We investigated study heterogeneity using a χ^2 test and calculation of an I^2 analog Bayesian statistic.[44]

Data Synthesis, Statistical Modeling, and Sensitivity Analysis

We performed full Bayesian probability modeling[20] of the population-averaged subject-specific effect[90] as

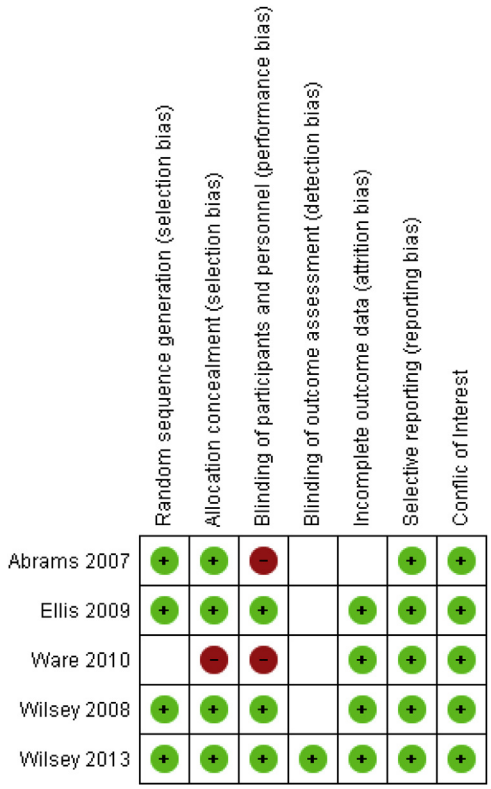

Figure 2. This summary of bias graph shows that the studies included were mostly of good quality in the domains of sequence generation, concealed allocation, incomplete outcome data, and selective reporting, and with regard to conflict of interest. However, the nature of the intervention likely interfered with effective blinding, possibly resulting in a high risk of performance bias in all studies and detection bias due to a lack of blinding of outcome observers. (Abrams 2007,[2] Ellis 2009,[31] Ware 2010,[81] Wilsey 2008,[85] Wilsey 2013[84]).

detailed in the statistical supplement (Supplementary Appendix 3). We pooled the treatment effects following a hierarchical random-effects Bayesian responder model. Kruschke[51] provided an accessible introduction to Bayesian methods in health sciences. Ashby[6] recently offered a chronological outline of applications in medicine, and Spiegelhalter et al[74] compiled the first concise overview. Gelman et al[35] described Bayesian hierarchical modeling approaches more formally. Supplementary boxes explain the basic concepts of Bayesian inference (Supplementary Boxes 1–3). The prior for the between-study variability (Cauchy) and the pooled effect estimate (normal distribution) were centered at zero with a standard deviation of 100. We preferred the Cauchy distribution over the closely related t-distribution, because the Cauchy is more robust in accommodating outliers[34,35]; these priors for our meta-analysis were uninformative and served to ensure computational convergence of the Markov chain Monte Carlo algorithm. Our priors were subsequently subjected to sensitivity analysis. Inference was implemented using a Gibbs sampling scheme to generate a computer simulation of a Monte Carlo sample from the posterior distribution in OpenBugs.[53] Our OpenBugs program code is provided in Supplementary Appendix 4. We have uploaded details on Monte Carlo Markov chain convergence, including graphs

demonstrating mixing, as supplementary material (Supplementary Figs 1 and 2). Differences in the design and quality of the studies were the focus of a sensitivity analysis. We tested the sensitivity of our results for our Bayesian model and its assumptions. We investigated our choice of prior and model parameters and reanalyzed the individual patient responder data 1) in a frequentist random-effects meta-analysis and 2) controlling for cannabis dose as an explanatory variable of the between-study variability in a meta-regression (methods and data not shown but available on request).

Reporting

We estimated the number needed to treat (NNT) and calculated the Bayes factor,[36] compared with the classic *P* values in Supplementary Box 3. We provided forest plots for the individual trials broken down by dose for the period level data (Fig 3). The reported pooled Bayesian estimate is the population-averaged subject-specific odds ratio comparing inhaled cannabis versus placebo for chronic painful neuropathy and their 95% Bayesian credible intervals ($CRI_{95\%}$), displayed as the standard diamond used for synthesized effects.[43]

Differences From the Initial Protocol

In our initial Prospero protocol registration, we considered including all types of studies, populations, and cannabis interventions. We intended to do a network analysis in 1 coherent Bayesian model. We found published aggregate data insufficient for evidence synthesis and therefore we decided to attempt an individual patient data meta-analysis, but limiting ourselves to only RCTs investigating inhaled cannabis, and updated the protocol accordingly.

Results

Our search (Fig 1) was completed in April 2014 and yielded 1738 references (1236 in MEDLINE, 359 in EMBASE, 123 in Cochrane Central, and 65 in AMED) matching the predefined search parameters. We excluded 118 duplicates and 1573 references for which we could clearly discern from the title or abstract that they were not randomized trials or did not investigate cannabis for a painful condition. Our hand search yielded no additional references. Except for the 5 studies included,[2,31,81,84,85] the remaining 163 publications studied different modes of cannabis administration or included participants with other painful conditions. No study investigated outcomes beyond 2 weeks. The characteristics of the 5 RCTs meeting our inclusion criteria are summarized in Table 1 and detailed characteristics are presented in Table 2. Important studies that were excluded are listed in Supplementary Table 2 with reasons for their exclusion.

Descriptive Characteristics of the Studies Included and the Participants

One hundred and seventy-eight middle-aged participants (approximately equal numbers of men and women) with painful neuropathy of at least 3 months duration (pain scores at least about 3/10) were enrolled in 5 RCTs executed across North America. Two trials recruited only HIV-positive individuals with HIV-related chronic painful neuropathy[1,2,31]; sexual orientation and

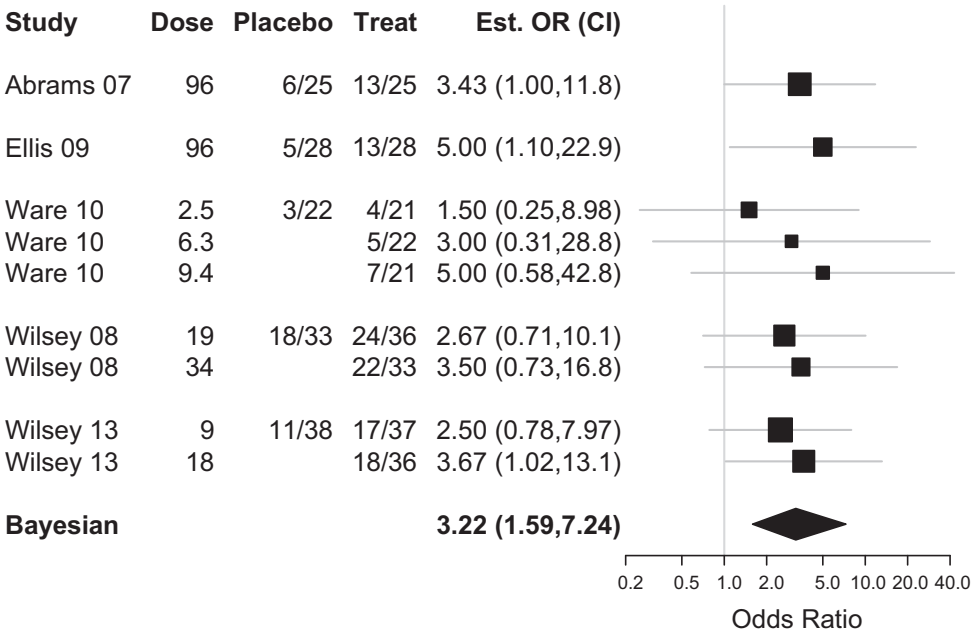

Figure 3. The forest plot displays odds ratios (with the 95% CRI indicated by horizontal bars on the log scale) to indicate their contribution to the Bayesian pooled effect estimate shown below as a diamond with the Bayesian 95% CRI. The table on the left lists the raw responder data at the study level. For Ware 2010,[81] Wilsey 2008[85] and Wilsey 2013,[84] the responder data are broken down by dose, listing the number of observed responses for each crossover period and the corresponding cannabis dose. The increased effect with increased cannabis content (evident in the period level data of Ware 2010,[81] Wilsey 2008,[85] and Wilsey 2013[84]) is additional evidence in support of the effect of cannabis on chronic painful neuropathy.

Table 1. Summary of the 5 RCTs on Inhaled Cannabis for Chronic Neuropathic Pain

Characteristic	Abrams 2007	Ellis 2008	Ware 2010	Wilsey 2008	Wilsey 2013
Neuropathy	HIV-DSPN	HIV-DSPN	Posttraumatic	Sensory	Mixed
Participants	50	34	23	38	39
Allocation	<---------- Randomized ---------->				
Intervention	<---------- Inhaled cannabis versus placebo ---------->				
Outcome	VAS	DDS	NRS	VAS	VAS
Follow-up	<---------- 5 days ---------->		2 weeks	<---------- 5–6 h ---------->	
Design	Parallel	<---------- Crossover ---------->			
Statistics	Mann-Whitney	Wilcoxon rank sum	<---------- General and linear mixed models ---------->		

Abbreviations: HIV-DSPN, HIV-related distal sensory polyneuropathy; DDS, Descriptor Differential Scale; NRS, Numerical Rating Scale.
NOTE. The cause of chronic neuropathic pain varied (including traumatic, central, diabetic, and HIV-related). Study authors used several patient-reported pain outcome instruments.

transgender data were not reported. Three trials recruited patients with neuropathy secondary to trauma,[81] spinal cord injury, diabetes mellitus, and complex regional pain syndrome.[84,85] Psychiatric disease, substance abuse, and significant cardiopulmonary disease were explicit exclusion criteria. Although previous cannabis experience was a prerequisite for inclusion for some studies,[1,2,84,85] current use was an exclusion criterion in all. Prescribed opioid use was not specified among the inclusion or exclusion criteria.

Characteristics of Interventions and Comparators

All studies investigated inhaled cannabis. The 5 studies used different doses, estimated as detailed in the Supplementary Table 3. All 5 studies used whole *Cannabis* plant provided by the US National Institute of Drug Abuse (NIDA). Cannabis was administered as prerolled cigarettes in 3 studies,[1,2,31,85] through a Volcano vaporizer in 1 study,[84] and as gelatin capsules smoked through a pipe at home in 1 study.[81] All 5 studies used identical-looking placebo as comparator. Concomitant nonstudy analgesics were permitted and continued in both arms.

Clinical Outcomes and Adverse Effects

All 5 RCTs reported continuous patient-reported spontaneous pain intensity scales as primary outcomes. We report the study level observed odds ratio (with 95% CRI indicted by vertical bars on the log scale) as a measure of their contribution to the Bayesian pooled effect estimate (shown as a diamond with 95% CRIs below) (Fig 3). The breakdown of responder data by dose suggested an increased effect with increased cannabis content.

Withdrawals due to adverse effects were rare. One case of serious adverse effects leading to withdrawal occurred in the placebo group (a case of psychosis) and 2 others in active treatment groups (hypertension and increased pain). Subjective side effects included anxiety, disorientation, difficulty concentrating, headache, dry eyes, burning sensation, dizziness, and numbness and were reported as being mild. Wilsey et al[85] reported short-term declines in attention, psychomotor performance, and learning and memory in the highest dose (7% tetrahydrocannabinol) group. Memory impairment was also seen in the placebo group and at lower doses, albeit at lower levels. Statistically significant physiological changes (such as increases in heart rate) were observed in one study[31] but not in another study.[81] Reports of euphoria or "high" were rare.[81] Psychoactive effects (such as feeling "high") were statistically significantly associated with treatment allocation in 2 studies[2,31] and increased in frequency with increasing dose[81,85]; they were mostly mild. The studies included followed patients only for days to weeks and hence did not report long-term adverse effects.

Study Design

All 5 studies were randomized, placebo-controlled, and double-blind; 4 used a crossover design[31,81,84,85] and 1 study used a parallel design.[1] Duration of follow-up varied from hours[84,85] to days[2,31] or weeks.[81]

Risk of Bias in the Studies Included

We characterized the risk of bias of the studies (Fig 2 and Supplementary Table 1). Randomization and allocation concealment were well described and suggested a low risk of bias. Ineffective participant blinding might have possibly resulted in performance bias in all studies; placebo effects are likely, when participants guessed their allocation, possibly leading them to overestimate the effect of inhaled cannabis on pain. Blinding of outcome observer was well described in 1 study,[84] and the use of patient diaries as an outcome instrument led us to estimate the risk of detection bias as unclear in the remaining studies. Incomplete outcome data were well described in all studies and are detailed in Table 2. Withdrawals potentially related to treatment effects led to a high risk of bias in 1 study[81] but did not seem to be associated with group allocation in all others.[2,31,84,85] All the trials included reported their primary outcome as specified in the protocol. We investigated publication bias in a funnel plot proposed by Egger et al,[29] because with fewer studies than 10 studies, the power of the tests is insufficient to distinguish chance from real asymmetry.[44] Studies received only public funding; all authors provided detailed conflicts of interest statements.

Evidence Synthesis of Effects

Based on data from 178 patients with a total of 405 observed responses, we estimated the odds ratio for more than 30% reduction in pain scores in response to

Table 2. Detailed Characteristics of the 5 RCTs Investigating Smoked or Inhaled Cannabis for Painful Neuropathy

Study ID	Year	Journal	Pubmed ID	Trial Registry ID
Abrams 2007[2]	2007	Neurology	17296917	NCT00046722
Population	55 HIV-positive adults with symptomatic HIV-DSPN and at least 30/100 VAS, on stable pain regimen for 8 weeks before enrolment, with previous experience of smoking cannabis randomized in 2 groups of size 27/28. Our Bayesian analysis is based on 50 participants with 1 observation per patient, as provided by the primary study authors. Age (experimental, control): 50 y (SD ± 6 y), 47 y (SD ± 7 y) Gender (male/female/other): experimental 22/5/0, control 26/2/0			
Intervention	Experimental: patient smoked 1 cigarette 3 times per d as tolerated Prerolled, whole-herb *Cannabis* cigarettes were provided by NIDA and contained 3.56% Δ-9-THC. Control: identical prerolled cigarettes with the active ingredient extracted. Dose estimate: 32 mg THC per session; 96 mg THC per d			
Primary outcome	Daily pain diary recording the VAS at 8 AM for average pain during the previous 24 h			
Study methods	Randomized, double-blind (patient, outcome assessor), parallel design, placebo-controlled, single-center (university) clinical trial in San Francisco, California, starting in 2003			
Notes	Also published as an abstract at the 2nd Annual Meeting of the International Association for Cannabis as Medicine, 2005 Secondary outcomes: acute analgesic effects; long thermal stimulation Anti-hyperalgesic effects: heat-capsaicin model; profile of mood states			
Ellis 2009[31]	2008	Neuropsychopharmacology	18688212	NCT00255580
Population	34 HIV-positive adults with symptomatic HIV-DSPN and pain score >5/20 on DDS, most participants were previously exposed to potentially neurotoxic deoxy-nucleoside reverse transcriptase inhibitors; 16 started control/experimental, 18 started experimental/control. 28 participants with a total of 56 observed responses were included in the Bayesian analysis Age (all): 49.1 y (SD ± 6.9 y) Gender (male/female/other): 33/1/0			
Intervention	Experimental: patient smoked cannabis, titrating dose up or down to obtain effective pain control/tolerable adverse effects, starting at 4% and ranging between 1 and 8% Δ-9-THC concentration by weight. Prerolled, whole-herb *Cannabis* cigarettes were provided by NIDA Control: identical prerolled cigarettes with the active ingredient extracted Dose estimate: average 96 mg THC per d			
Primary outcome	Crossover difference in change of DDS 0–20 scale "a ratio scale containing 24 words describing pain intensity and unpleasantness" comparing baseline with after treatment			
Study methods	Randomized, double-blind (patient, outcome assessor), crossover design, placebo-controlled, single-center (university) clinical trial at the University of California, San Diego, California, in 2006			
Notes	Secondary outcomes: McGill questionnaire, VAS, Sickness Impact Profile, Brief Symptom Inventory, UKU side effect rating, Highness/Sedation Scale, HIV load			
Ware 2010[81]	2010	Canadian Medical Association Journal	20805210	ISRCTN68314063
Population	23 adults with non-HIV neuropathy pain of at least 3 mo duration caused by trauma or surgery defined by pain intensity score greater than 40/100 VAS, on a stable analgesic regimen, not having smoked cannabis in the preceding year. 23 participants with a total of 86 observed responses were included in the Bayesian analysis Age (all): 45.4 y (SD ± 12.3 y) Gender (male/female/other): 11/12/0			
Intervention	Experimental: NIDA and Prairie plant systems prepared 3 different potencies of THC (2.5%, 6%, 9.4%) from whole herb in gelatin capsules inhaled through a pipe Control: ethanolic extraction was used to prepare the placebo Dose estimate: 0, 1.625, 3.9, and 5.85 mg/d (average) THC per period			
Primary outcome	Average daily pain intensity on the 11-item NRS averaged over 5 treatment d (least pain value, average pain value, and worst pain value) during 4 consecutive crossover periods of 14 d each (5 treatment d and 9 washout d afterwards)			
Study methods	Randomized, double-blind (patient, outcome assessor), 4-period crossover Latin square design, placebo-controlled, single-center (university) clinical trial in McGill University, Montréal, Canada, starting in 2003			
Notes	The linear model did not consider interparticipant effects Secondary outcomes: pain quality, McGill questionnaire, sleep (Leeds Sleep Evaluation Questionnaire); mood effects, short-form Profile of Mood States; quality of life: EQ-5D health outcomes			
Wilsey 2008[85]	2008	The Journal of Pain	18403272	NCT00254761
Population	38 adults with non-HIV neuropathy (complex regional pain syndrome (type I), spinal cord injury, peripheral neuropathy, or nerve injury) with previous cannabis experience and a VAS >30/100. 38 participants with 102 observed responses were included in the Bayesian analysis Age (all): 46 y (range 21–71 y) Gender (male/female/other): 20/18/0			

Table 2. Continued

Study ID	Year	Journal	Pubmed ID	Trial Registry ID
Intervention	Experimental participants inhaled a total of 9 standardized cued puffs. Cannabis was harvested from whole plant and rolled into cigarettes at the University of Mississippi under supervision of NIDA ranging in strength from 0% to 3.5–7%. Control: placebo cigarettes were made from whole plant with extraction of *Cannabis* Dose estimate: 0 placebo, 19.25 (low dose, range 7–30.45), 34.3 (high dose, range 18.9–60.9) mg THC/d (session)			
Primary outcome	VAS measuring spontaneous pain relief; time effects were studied with a linear model			
Study methods	Randomized, double-blind (patient, outcome assessor), parallel design, placebo-controlled, single-center (university) clinical trial at University of California Davis Medical Center, Sacramento, California, started in November 2003			
Notes	Secondary outcomes: pain unpleasantness (VAS), heat pain threshold, Neuropathic Pain Scale, neurocognitive assessment, and plasma *Cannabis* concentration			
Wilsey 2013[84]	2013	The Journal of Pain	23237736	NCT01037088
Population	39 adults with non-HIV neuropathy due to reflex sympathetic dystrophy, peripheral neuropathy, postherpetic neuralgia, poststroke pain, multiple sclerosis, or spinal cord injury with previous cannabis exposure (16 current, 23 ex-users) and a VAS pain intensity greater than 30/100. 39 participants with 111 observed responses were included in the Bayesian analysis Age (all): 50 y (SD ± 11 y) Gender (male/female/other): 28/11/0			
Intervention	Experimental: participants used a volcano vaporizer under the flexible-dose design of Wilsey 2008. The minimum and maximum cumulative doses for each visit were 8 and 12 puffs. Cannabis was harvested at the University of Mississippi under the supervision of NIDA Control: placebo was made from whole plant with removal of cannabinoids Dose estimate: maximum of 0, 10.32, 28 mg THC/d (session), presuming they were administered the entire 800 mg dose			
Primary outcome	VAS before and after consuming vaporized cannabis			
Study methods	Randomized, double-blind (patient, outcome assessor), crossover design, placebo-controlled, single-center (university) clinical trial at the University of California, Davis, California, started December 2009			
Notes	Secondary outcomes: Patient Global Impression of Change; Neuropathic Pain Scale; WAIS-III, Hopkins Verbal Learning Test (revised), Grooved Pegboard Test			

Abbreviations: HIV-DSPN, HIV-related distal sensory polyneuropathy; SD, standard deviation; DDS, Descriptor Differential Scale; NRS, Numerical Rating Scale.
NOTE. Two trials recruited patients with HIV-DSPN, 3 included participants with neuropathies due to other causes.

inhaled cannabis versus placebo for chronic painful neuropathy as 3.2 with a Bayesian CRI (subsequently denoted with the subscript $_{CRI95\%}$) $[1.59, 7.24]_{CRI\ 95\%}$, and the NNT as 5.55 $[3.35, 13.7]_{CRI\ 95\%}$. We estimated the posterior probability of the effect of *Cannabis* for chronic painful neuropathy to be 99.7% and the Bayes factor as 332 (Fig 3). The Bayesian analog I^2 statistic was 0. The posterior probability that the between-study variability in effects was greater than what would be expected by chance is .45. Effects seemed to increase with tetrahydrocannabinol (THC) content supporting the effect of cannabis for chronic painful neuropathy as seen in the forest plot (Fig 3). Specifically, the increased effect with increased cannabis content (evident in the period level data of Ware 2010,[81] Wilsey 2008[85] and Wilsey 2013[84]) is additional evidence consistent with the effect of cannabis for chronic painful neuropathy. However, a meta-regression of cannabis dose (data not shown but available on request) did not change our estimates or inferences. The aggregate and individual data on adverse effects were too sparse to be pooled. Model convergence is documented in the supplementary material (Supplementary Figs 1 and 2).

Sensitivity Analysis

When we performed a sensitivity analysis (available on request) with regard to differences in the quality of studies, we found effect estimates and credible intervals to be robust regarding the inclusion or exclusion of any single study. Our inferences were rather insensitive to priors (between-study variance) in our Bayesian model (Supplementary Box 2). Reanalyzing the data in a frequentist random-effects meta-analysis did not change the results.

Discussion

Our evidence synthesis of individual patient data from 178 participants with 405 observations in 5 RCTs with a follow-up ranging from days to weeks (Fig 3) provides evidence that inhaled cannabis results in short-term reductions in chronic neuropathic pain for 1 in every 5 to 6 patients treated (NNT 5.6 with a Bayesian 95% CRI ranging between 3.4 and 14); based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definition of at least moderate benefit,[28] inhaled cannabis improved pain by an odds ratios of 3.2 (Bayesian 95% CRI of $[1.6, 7.2]_{CRI\ 95\%}$ (Fig 3). The Bayes factor was 332, corresponding to a posterior probability of effect of 99.7%.

We infer that this effect applies equally across chronic painful neuropathies of different causes (eg, diabetic and traumatic chronic painful neuropathy or HIV-related distal sensory neuropathy). The effects are remarkably homogeneous across studies (Bayesian I^2 analog = 0%) (Table 1). Dose dependency further supports the notion of a cannabis effect on neuropathy (Fig 3 and Supplementary Table 3). Our results (NNT 5.6 $[3.4, 14]_{CRI\ 95\%}$) suggest that inhaled cannabis may be about as potent as gabapentin (Cochrane Review

update: NNT 5.9 [4.6, 8.3]$_{CI\ 95\%}$ for diabetic neuropathy, Moore 2014[62]). The NNT of inhaled cannabis could potentially rival currently available therapeutics for chronic neuropathic pain,[82] whose NNT typically range well above 8, if there is any evidence at all.[15,21,25] However, we caution that our findings await confirmation in long-term pragmatic community-based trials. Our findings are remarkable considering the dearth of effective treatment options for chronic painful neuropathies or chronic pain in general.[49]

Our Review Enhances the Existing Literature on Treatment for Chronic Neuropathic Pain

Our evidence synthesis contradicts, updates, or complements the finding of several older and more recent reviews on cannabis by providing a meta-analysis for chronic neuropathic pain,[13,14,85] by updating evidence,[13-16] or by broadening the scope. We were able to include recent RCTs, not published or accessible to the previous reviews by Campbell, Phillips, Iskedjian, Lutge, or Lynch.[19,47,54,55,67] Compared with previous studies,[67] our meta-analysis of individual patient data and the inclusion of additional and recent clinical trials, which augmented the power to detect an effect, if it existed, and amplified the confidence in the pooled effect estimate (NNT = 5.6) by shrinking the 95% CRI,[2,3,12] our posterior probability of the short-term effects of inhaled cannabis is now very high (99.7%). Our analysis complements the recent evidence synthesis of cannabis for certain other neurological conditions by the American Academy of Neurology, which did not investigate cannabis for chronic neuropathic pain,[49] and supports another narrative review (published after submission of this manuscript) with a meta-analysis of individual patient data,[45] which concluded that "Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence."

Strength

Meta-analysis of Individual Patient Data Increased the Power of our Meta-analysis

We performed an individual patient meta-analysis. Unlike conventional meta-analysis based on published aggregate data, meta-analysis of individual patient data synthesizes the individual participants' original data obtained from the studies' principal investigators.[43] Meta-analysis of individual patient data is arguably the gold-standard of evidence synthesis,[71,75] not just because it allows for detailed data checking but because meta-analysis is often not feasible using only summary data. Synthesizing the diversity of reported outcomes of studies on inhaled cannabis for chronic painful neuropathy was a significant challenge for previous reviews.[13-16] In our review insufficient published outcome data and variations in design and outcome reporting would have led to the exclusion of relevant trials, because the published aggregate data lacked the necessary detail for pooling in a meta-analysis.[4,84,85]

The meta-analysis of individual patient data and the inclusion of additional recently published RCTs increased the power of our evidence synthesis and greatly increased the confidence in the effect of inhaled cannabis for chronic neuropathy compared with previous reviews.[46,54,55,67] The Bayesian posterior probability of more than 99.7% indicates the very high likelihood that inhaled cannabis is effective in the short term for 1 in 5 or 6 patients with chronic neuropathic pain (Supplementary Box 1), unlike the classic *P* value, which indicates how unlikely the observed outcomes data are given a null hypothesis of no effect. To our knowledge, this is the first Bayesian meta-analysis of individual patient data in medicine.[6]

The Observed Short-Term Effect of Inhaled Cannabis Is Meaningful for 1 in 5 or 6 Patients With Chronic Neuropathy

Our responder analysis is showing a statistically significant and minimal clinically important difference for 1 in 5 to 6 patients, an effect measure easily understood by patients, payers, and providers alike.[58] Responder analysis has been advocated for patient-reported outcomes in chronic pain trials to distinguish a minimal but statistically significant difference between groups on a population basis from a clinically meaningful effect for the individual participant.[28,60,61] Our cutoff for a meaningful response (>30%) is 1) grounded in what patients themselves judge to be important improvement[32] and 2) based on expert consensus (IMMPACT).[58] Based solely on frequentist hypothesis testing, responder analysis may miss the goal, while losing power.[72] Our Bayesian meta-analysis of individual patient data allowed us to calculate a posterior probability of effect larger than 99.7%.

Limitations

Effects Are Consistent Across Different Causes and Populations

We pooled data from populations with chronic painful neuropathy of different causes and in different populations. We included HIV-related distal sensory polyneuropathy, posttraumatic, complex regional pain syndrome, peripheral and diabetic peripheral neuropathy, and patients with and without previous exposure to cannabis. Similar approaches were also taken by authors of previous reviews on cannabis for chronic painful neuropathy.[13-16] Evidence synthesis across distinct but closely related painful neuropathies is reasonable because their clinical course and pathological mechanism are considered similar and receive uniform treatment recommendations[9,64]; Indeed, the "etiological factors responsible for driving the mechanisms are not disease specific" and "disease diagnosis is not helpful in selecting the optimal pain therapy".[86,87] Even if the absence of evidence for heterogeneity constitutes no evidence for clinical homogeneity,[44] the consistency and uniformity of the effect of inhaled cannabis on chronic neuropathic pain across different causes and

populations, further enhances our confidence in the generalizability of our findings.[48] Yet, our meta-analysis can only be as strong as the underlying data (Tables 1 and 2) and the methodological quality (Fig 2 and Supplementary Table 1); the small number of studies included, their small number of participants, and shortcomings in allocation concealment[42] and attrition (Table 2) limit our ability to draw firm conclusions. The small numbers of studies found in each subgroup precluded a formal study of publication bias. A graphical analysis or the test proposed by Egger et al[29] should at least include 10 studies because, with fewer studies, the power of the tests is insufficient to distinguish chance from real asymmetry.[44] We find that the use of an active placebo to mimic the psychotropic effects of experimental treatments, although it improves blinding, does not necessarily improve the evidence regarding effectiveness in a pragmatic clinical setting, but it does acknowledge the risk of performance bias.[70] Also meta-analyses of sparse data can be unstable[38,66]; however, our evidence synthesis is based on individual patient data from all included trials, the best available source of evidence, short of a large RCT.[44,76]

Cannabis Dose and Mode of Administration May Influence Pain Relief

Estimating bioavailable cannabis is difficult. Many factors influence the amount of THC per cigarette, particularly whether the material is dry or freshly picked (Supplementary Table 3). The dose delivered likely differs from what is actually ingested[69]; we validated our dose estimates with the primary authors of the studies included. In the forest plot of the raw responder data, a higher dose seems to be associated with a stronger effect (Fig 3). Our sensitivity analysis controlling for cannabis dose only marginally improved the precision (data not shown); hence, at the individual patient level, the dose differences did not explain the differences in effect. This may effectively reflect the individual dose titration.

We cannot comment on long-term adverse effects because the available trials followed their patients for a maximum of 2 weeks.[3] Recently, several authors have raised concerns about driving while intoxicated, withdrawal, addiction, adverse cardiovascular, pulmonary and cognitive effects, especially in the developing brain, although several of these misgivings remain contentious.[11,16,17,26,37,40,47,68,77,83,88] Extrapolating from recreational use is problematic and the risk-benefit balance differs when pain is medically intractable. Clearly, we need to learn more about the benefits and risk associated with long-term cannabis use.

Our Bayesian Meta-analysis Is Robust to Parameter Choices and Model Assumptions

Bayesian methods are sometimes critiqued for their presumed subjectivity, but the short-term effects of inhaled cannabis for about 1 in 5 patients with chronic neuropathic pain are robust and independent of our mode of evidence synthesis. Our assumptions are modeled explicitly and tested.[14] Priors for our meta-analysis were uninformative in order to minimize subjectivity and just served to ensure computational convergence. As detailed in the results and illustrated in Supplementary Box 2, when subjected to sensitivity analysis, our findings were robust to the choice of parameters and models. Unsurprisingly, running a frequentist analysis resulted in similar estimates, except that the CRIs of our Bayesian estimate were more conservative because they were based on more cautious between-study variance estimates. Obviously, the Bayesian approach provides a posterior probability (99.7%; for the short-term benefits of inhaled cannabis for about 1 in 5 patients with chronic neuropathy), an inference not possible in the frequentist paradigm.[74] The result of any meta-analysis will critically depend on this estimate of the between-study variance. Our between-study variability estimation was more conservative than the classic random-effects approach promoted by the Cochrane Collaboration,[43] which itself is more conservative than the often employed fixed effects model. Indeed, the continued debate on fixed versus random-effects models, concerns about assumptions, and underestimation of between-study variability[24] demonstrate that the classic "frequentist" statistical approach is also not free of subjectivity.[78] The use of subjective model parameters destroys the illusion of objectivity in "frequentist" as well as in meta-analysis.[78] Our Bayesian approach transparently included any subjective choice explicitly in our model and subjected all to sensitivity analysis.[22,66]

Recommendations for Future Research

We lack long-term pragmatic clinical trials to determine if the effects of cannabis on chronic painful neuropathy are sustained and durable, if cannabis use is feasible in the community given the associated stigma,[1,18] if cannabis can be safely prescribed in vulnerable and young populations,[26,77] and if long-term adverse effects outweigh the benefits of inhaled cannabis.[11,40,47,68,77] Although the cost of inhaled cannabis is likely to be low, medicinal cannabis continues to be controversial (indeed illegal in many jurisdictions) and patients may vary in their preferences on inhaling cannabis, especially as long as it remains stigmatized. We need to investigate if individual titration allows for the best balance of beneficial to adverse effects. The effects of cannabis for other conditions should equally be explored in publicly funded rigorous RCTs. Solid clinical evidence may facilitate selective prescribing, prevent misuse, and reduce opioid-related harms.[41]

Conclusions

Our meta-analysis of individual patient data suggests that inhaled cannabis results in short-term benefits for chronic neuropathic pain with an NNT of 5.6 [3.4, 13]$_{CRI95\%}$ (Fig 3). We lack evidence regarding sustained long-term benefits and risks in the community setting. The small number of studies and participants included in the analysis (Table 1) and the risk of detection and

performance bias weaken our ability to draw firm conclusions (Fig 2). In our responder analysis of the proportion of patients with at least 30% reduction in chronic pain as the minimal clinically important difference, a meaningful improvement at the individual patient level was found for about 1 in every 5 to 6 patients treated.[27,58] This effect on chronic painful neuropathy is consistent across diverse causes, all hitherto resistant to available treatments (Table 1). To our knowledge, ours is the first Bayesian meta-analysis of individual patient data. The Bayesian modeling approach may be flexibly extended to other fields and questions where variance in outcome reporting hampers the classic approach to meta-analysis.[6,7,78]

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2015.07.009.

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