Hawai'i Journal of Medicine & Public Health

A Journal of Asia Pacific Medicine & Public Health

April 2014, Volume 73, No. 4, ISSN 2165-8218 EDITORIAL: THE CANNABIS CONUNDRUM Michael J. Meagher MD THE CURRENT STATUS OF MEDICAL MARIJUANA IN THE UNITED STATES Gerald J. McKenna MD THERAPEUTIC BENEFITS OF CANNABIS: A PATIENT SURVEY Charles W. Webb MD and Sandra M. Webb RN, BSN PARANEOPLASTIC SYNDROME IN HAWAI'I: A CASE OF DERMATOMYOSITIS ASSOCIATED WITH ENDOMETRIAL CANCER Cherisse Wada MSIII; Charles N.C. Hua MS, MSIII; and Michael E. Carney MD

MID-VENTRICULAR VARIANT TAKOTSUBO CARDIOMYOPATHY ASSOCIATED WITH CANNABINOID HYPEREMESIS SYNDROME: A CASE REPORT 115 Magazulki Nagi MD: David Forgusaga MD: and John Michael Chua Chiaga MD

Masayuki Nogi MD; David Fergusson MD; and John Michael Chua Chiaco MD

MEDICAL SCHOOL HOTLINE The Pacific Basin Rehabilitation Research and Training Center at the John A. Burns School of Medicine: Thirty Years of Service to Hawai'i and Beyond

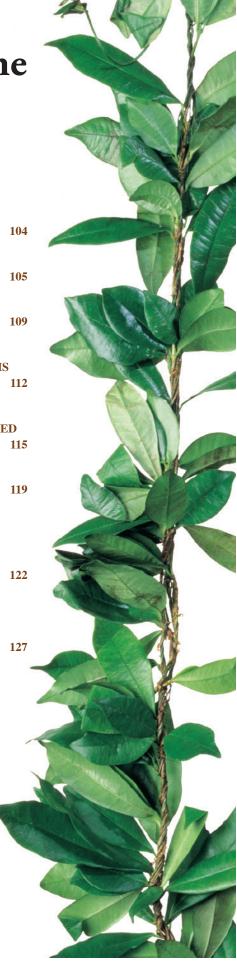
Violet E. Horvath PhD, MSW, MFA

INSIGHTS IN PUBLIC HEALTH

Perspectives on Pain in the Low Back and Neck: Global Burden, Epidemiology, and Management
Maria Vassilaki MD, PhD, MPH and Eric L. Hurwitz DC, PhD

THE WEATHERVANE

Russell T. Stodd MD



Partners in Sustainable Health Care



HMSA's objective in implementing the patient-centered medical home (PCMH) model is to build a sustainable health care system for Hawaii. In collaboration with key stakeholders, HMSA is encouraging its members to select and use a PCP.

If you would like to participate in HMSA's PCMH program, please call PCMH Practice Transformation Manager Cynthia Lum at 948-6058 on Oahu.

We strive every day to ensure that our members have access to quality health care delivered by the state's largest network of providers. Through collaboration with providers and provider organizations, we are able to create opportunities for improvement in the quality of care provided to our members. We appreciate your work effort and look forward to a bright future for Hawaii's health care system and the health of our members.



An Independent Licensee of the Blue Cross and Blue Shield Association

Hawai'i Journal of Medicine & Public Health

A Journal of Asia Pacific Medicine & Public Health

ISSN 2165-8218 (Print), ISSN 2165-8242 (Online)

The Journal's aim is to provide new scientific information in a scholarly manner, with a focus on the unique, multicultural, and environmental aspects of the Hawaiian Islands and Pacific Rim region.

Published by University Clinical, Education & Research Associates (UCERA)

Hawai'i Journal of Medicine & Public Health 677 Ala Moana Blvd., Suite 1016B Honolulu, Hawai'i 96813 http://www.hjmph.org Email: info@hjmph.org

The Hawai'i Journal of Medicine & Public Health was formerly two separate journals: The Hawai'i Medical Journal and the Hawai'i Journal of Public Health. The Hawai'i Medical Journal was founded in 1941 by the Hawai'i Medical Association (HMA), which was incorporated in 1856 under the Hawaiian monarchy. In 2009 the journal was transferred by HMA to University Clinical, Education & Research Associates (UCERA). The Hawai'i Journal of Public Health was a collaborative effort between the Hawai'i State Department of Health and the Office of Public Health Studies at the John A. Burns School of Medicine established in 2008.

Editors:

S. Kalani Brady MD Michael J. Meagher MD Editor Emeritus: Norman Goldstein MD Associate Editors: Donald Hayes MD, MPH Kawika Liu MD Jay Maddock PhD Copy Editor:

Public Health Manuscript Editors:

Tonya Lowery St. John MPH Ranjani R. Starr MPH

Contributing Editors:

Alfred D. Morris MD

Satoru Izutsu PhD

Russell T. Stodd MD

Carl-Wilhelm Vogel MD, PhD

Layout Editor & Production Manager:

Drake Chinen

Subscription Manager:

Meagan Calogeras

Editorial Board:

Benjamin W. Berg MD, Patricia Lanoie Blanchette MD, S. Kalani Brady MD, John Breinich MLS, John J. Chen PhD, Donald Hayes MD, MPH, Satoru Izutsu PhD, Kawika Liu MD, Tonya Lowery St. John MPH, Jay Maddock PhD, Douglas Massey MD, Michael J. Meagher MD, Alfred D. Morris MD, Myron E. Shirasu MD, Ranjani R. Starr MPH, Russell T. Stodd MD, Frank L. Tabrah MD, Carl-Wilhelm Vogel MD

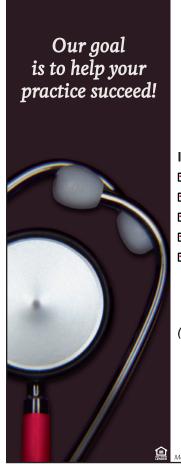
Statistical Consulting:

Biostatistics & Data Management Core, John A. Burns School of Medicine, University of Hawai'i (http://biostat.jabsom.hawaii.edu)

Advertising Representative

Roth Communications 2040 Alewa Drive, Honolulu, HI 96817 Phone (808) 595-4124

The Hawai'i Journal of Medicine & Public Health (ISSN 2165-8218) is a monthly peer-reviewed journal published by University Clinical, Education & Research Associates (UCERA). The Journal cannot be held responsible for opinions expressed in papers, discussion, communications, or advertisements. The right is reserved to reject material submitted for editorial or advertising columns. Print subscriptions are available for an annual fee of \$220; single copy \$20 includes postage; contact the Hawai'i Journal of Medicine & Public Health for foreign subscriptions. Full text articles available on PubMed Central. ©Copyright 2014 by University Clinical, Education & Research Associates (UCERA).



Come and find out how.

Preferred loan programs for Medical Professionals like you!

If you are interested in:

- **☑** Buying an existing practice
- **⊠** Expanding a practice
- **☑** Purchasing or leasing equipment
- ☑ Purchasing commercial property
- **☑** Refinancing existing loans, etc...

We can help!

Visit any of our branches or call (808) 528-7711 for more information.



Where Your Business Comes First www.HawaiiNational.com

Member: FDIC/Federal Reserve System Equal Opportunity Lender

Over 50 Years of Dedication to Hawai'i's Physicians

The Board of Directors at Physicians Exchange of Honolulu invite you to experience the only service designed by and for Physicians in Hawaii.

President:

Myron Shirasu, M.D.

Vice President: Derek Ching, M.D.

Secretary:

Kimberly Koide Iwao, Esq.

Treasurer:

Richard Philpott, Esq.

Directors:

Melvin Inamasu, M.D. Robert Marvit, M.D. Stephen Oishi, M.D. Ann Barbara Yee, M.D. David Young, M.D.

Executive Director: Rose Hamura

- Professional 24 Hour Live Answering Service
- Relaying of secured messages to cell phones
- · Calls Confirmed, Documented and Stored for 7 Years
- HIPAA Compliant
- Affordable Rates
- · Paperless Messaging
- Receptionist Services
- · Subsidiary of Honolulu County Medical Society
- Discount for Hawai'i Medical Association members

"Discover the difference of a professional answering service. Call today for more information."

Physicians Exchange of Honolulu, Inc. 1360 S. Beretania Street, #301 Honolulu, HI 96814

(808) 524-2575

EDITORIAL

The Cannabis Conundrum

Michael J. Meagher MD, Co-Editor; Hawai'i Journal of Medicine & Public Health

There is little that engenders more argument and polemic than a discussion of the legalization of Marijuana usage. As of this writing 21 states allow use of Cannabinoids for medical use and 2 states allow recreational use. In 2000, the State of Hawai'i passed Bill 862, allowing the medical use of Marijuana for patients possessing a signed statement from their physician stating that he/she suffers from a debilitating condition and the "potential benefits of the use of Marijuana would likely exceed the health risks." The law underwent minor amendment in 2013. The two articles presented in this issue represent, we believe, opposing perspectives on the use of this drug, similar to the

arguments in the peer reviewed medical literature.² Drs. Webb and McKenna clearly disagree and espouse their positions clearly but do seem to agree on one thing: the data is insufficiently clear to render a single, evidence based position and considerably more research is needed.

For the present, we leave it to the reader to sort fact from value judgement: reference 2 is an ideal place to start.

References

- 1. http://www.Procon.org. Summary chart.
- Medical Use of Marijuana. NEJM. 2013;368;866-868. Available online as www.nejm.org/doi/ full/10.1056/NEJMcide1300970.

Document storage and security is best left to the experts.

Access can help protect your valuable information with safe storage and secure shredding and information destruction services. We're the leader in records and information management in Hawaii and throughout the United States.

Call your local Access Client Care Representative today at 1 877 FileLine.



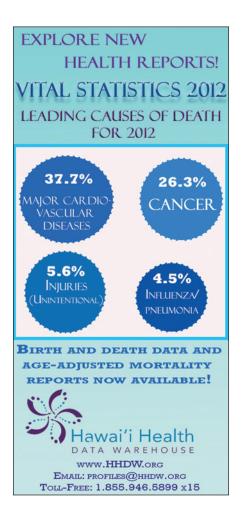




InformationProtected.com | 1 877 FileLine

Records and Information Management
Temperature and Humidity Controlled Media Vault
Secure Shredding | Destruction
Digital Solutions | Scanning | Web-Hosted Storage

Access is the only NAID-certified (National Association for Information Destruction) operation in Hawaii certified for plant and mobile destruction



The Current Status of Medical Marijuana in the United States

Gerald J. McKenna MD

Abstract

Medical marijuana is currently a controversial issue in medicine. There are strong pro and con opinions but relatively little scientific data on which to base medical decisions. The unfortunate scheduling of marijuana in class I has limited research and only serves to fuel the controversy.

This article will review the history of laws to regulate drugs in the United States in the 20th century to provide context for the current status of medical marijuana.

It will include the rationale for opposing medical marijuana laws and the problem of the Schedule I inclusion of marijuana as well as other drugs. It will examine the problems associated with smoking raw marijuana and review other routes of administration.

Finally, it examines the inadvisability of medicine's promotion of smoked marijuana.

Introduction

The regulation of mind-altering drugs in the United States has been steadily expanding since the early 20th century. It is necessary to briefly review this history in order to place in context the current status of marijuana, and medical marijuana in particular.

The 20th century saw several laws designed to restrict specific classes of drugs from unregulated use in the United States.

In 1909, the first law specifically banning a substance was passed to outlaw opium smoking.¹ The only groups in the United States smoking opium on a routine basis were Chinese immigrants, mostly in San Francisco and in other West Coast locations. This law had strong racial overtones. The United States did not want Chinese immigration and there was popular support to contain such immigration.

The Harrison Narcotics Act, passed by Congress in 1914, was a broader based ban. It specifically regulated a class of drugs, the opiates, from being grown or distributed. Opiates could then only be prescribed by physicians. The prior over-the-counter purchase of opiate products, mostly morphine, was banned. Interestingly, cocaine was included under the Act even though it was not an opiate.

The 18th amendment to the Constitution, the Volstead Act, banning the sale, production and transportation of alcohol in the United States, was passed in 1919. "Prohibition," coordinated by the Anti- Saloon League, became the law of the land.^{1,2}

Widespread smuggling of alcohol from Canada, the Caribbean, Mexico, and South America made the ban impractical. The failure of this law to limit alcohol's negative impact on society, the continued availability of alcohol, and the law's unpopularity led to the repeal of prohibition in December 1933 with the ratification of the 21st amendment to the Constitution.³

Heroin, an opiate that was regulated in the Harrison Narcotic Act, was specifically prohibited for use in the United States by another law in 1924.¹

The Marijuana Tax Act was passed in 1937. This act made it illegal to grow or distribute marijuana unless the grower obtained

a federal stamp. However, stamps were unavailable as there was no application process. Marijuana was therefore effectively outlawed by the necessary stamp being made unavailable.¹

The Controlled Substances Act of 1970 placed a number of mind-altering agents in Schedule I as they became available, including marijuana, Lyseric Acid Diethylamide (LSD), Gamma-Hydroxybutyrate (GHB), and now the various mephadrones in "bath salts."

These legislative actions have led to the gradual criminalization of an increasing percentage of American citizens, who continue to use the banned substances despite the laws passed to make them illegal. Accordingly, the country saw increased incarceration of nonviolent offenders, including both addicts and dealers, for drug-related offenses. The top dealers were rarely affected, as they were protected by many layers of internal drug trafficking bureaucracy. This has resulted in a greater percentage of the US population being incarcerated than any other country, creating enormous expense to taxpayers while having little effect on the use of or addiction to banned substances. The United States has 5% of the world's population but 25% of the world's incarcerated individuals.⁵

Looking back at laws passed here and elsewhere to control drug use, one can reasonably conclude that they have been ineffective.

Marijuana in the Vietnam War

Prior to regulation, marijuana was primarily used by small groups of people in the United States. Prior to the Controlled Substances Act of 1970, there was a marked increase in marijuana use during the '60's counterculture. These included "hippies" in the mid-1960s, college students, and faculty, and protesters in the antiwar movement.

There was a similar increase in marijuana use among military personnel serving in Southeast Asia throughout the Vietnam War. This use of marijuana, and later heroin, alarmed base commanders and eventually led to action by the Nixon administration and the passage of the Controlled Substances Act.⁴ Military authorities established detoxification facilities in Saigon and a program of drug urinalysis testing began in 1971 to identify persons using marijuana or other drugs.

An early attempt at identifying drugs in the urine, the unreliable free radical assay technique or FRAT test, included many false positives and incorrectly labeled many nonusers as drug users if they tested positive.

During the Vietnam War, I served as a psychiatrist at a US Air Force (USAF) Base in Thailand. Those who tested positive on the FRAT test were strapped to a stretcher and shipped to Saigon for detoxification. This sometimes led to the embarrassing misidentification and labeling as addicts service men

and women who had never used any drugs but turned up false positive on this test (personal experience, Chief Psychiatry, 11th USAF Hospital, U-Tapao Thailand 1970-71).

Marijuana use, however, has been widespread by many groups from the 1970s onward.

Medical Use of Marijuana

Marijuana was used as a medicinal for thousands of years and perhaps longer. The earliest written reports of marijuana use come from Chinese writings in the 27th century BC.

Until the early 1940s in the United States, marijuana was found in more than 20 medications for a variety of ailments. It continued to be included in the US Pharmacopoeia, the predecessor of the Physician's Desk Reference, five years after the Marijuana Stamp Act was passed.

Prior medical use of marijuana was restricted to extracts of the cannabis plant combined with various other ingredients and sold in a variety of patent medicines advertised and marketed as cure-alls. None of these "medicines" were smoked.

In states where medical marijuana is currently available, it is almost exclusively sold in drug emporiums in a raw state meant to be smoked. In Hawai'i, individuals with medical marijuana cards were initially allowed to cultivate three plants for personal use; this later increased to seven plants.

The vast majority of medical marijuana users claim chronic pain and smoke the raw plant. (A small group use marinol, a legal medical form of tetrahydocannibol, prescribed in a 5mg tablet, which has a little or no euphoric properties.)

The scheduling by the Drug Enforcement Agency of marijuana and other drugs (heroin, Lysergic Acid Diethylamide, Gamma-Hydroxybutyrate, and various mephadrones in "bath salts") automatically eliminates valid research on the drugs, which is never a good idea from an academic, research, or public policy perspective.

Marijuana should be removed from Schedule I. This would allow research to determine possible medical applications of marijuana extracts and develop acceptable delivery methods other than smoking the raw plant.

In Hawai'i, the Hawai'i Medical Association (HMA) took a stance against the first medical marijuana bill passed in 2000. One main sticking point is that medical marijuana would need to be provided in a non-smoking form in order to have support from the medical profession. Authorizing use by inhalation of a drug with an unknown number of co-drugs contained in the same raw form is not supportable.

The United States has experienced a century of terrible adverse medical consequences of cigarette smoking and nicotine addiction. Over 400,000 lives lost each year are directly and indirectly attributable to the adverse effects of smoking cigarettes. We endured as a nation, and as a medical profession, the falsification of data from the US tobacco industry regarding the problems of nicotine use and, specifically, the problems related to chronic inhalation of a raw drug which contained nicotine and multiple other identified tars and carcinogens. How can physicians or medical associations support any medical mari-

juana law that involves smoking an unrefined drug after this experience with cigarette smoking?

Marijuana's ingredients are available in a pill form. The approval of Marinol, a non mind-altering form of delta 9 tetrahydrocannabinol for general use, is a case in point. This is a marijuana extract that has been available by physician prescription for use for a variety of anecdotally acceptable treatments, especially the nausea associated with chemotherapy, anorexia associated with HIV infection, and some reported forms of pain relief. Other ingredients from the cannabis plant have been isolated and found to be anecdotally useful in treating certain childhood seizure disorders.

Supporting the use of medical marijuana by inhalation solely because users prefer it would be akin to supporting the inhalation of any other drug meant to be taken by mouth. Addicts in our treatment program often crumble pills and nasally inhale or inject them intravenously to obtain a faster high. We would never say, "OK, go ahead and inject yourself if that's what you prefer."

The primary reason for medical marijuana use is control of chronic pain. Medical users descriptions of chronic pain are often vague and may relate to some distant injury or surgery to rationalize the need for a marijuana card in Hawai'i.

Some practicing physicians in Hawai'i who formerly prescribed the marijuana card have ceased doing so (anonymous, personal communication). A few physicians travel within the state for the purpose of writing marijuana prescriptions. Many neither examine the patient nor take a detailed history.

Marijuana card holders who seek addiction treatment in our program for marijuana dependence indicate that at the time of prescription, they in fact had very little pain. They told the prescribing physician what was necessary to obtain a medical card. They also report minimal history taking or physical examination by the physician. Rarely were they required to show some evidence that indicated pathology. It is difficult to support that approach to prescribing any medication.

Most pain medicine specialists emphasize the importance of understanding the pathophysiology, severity, and origin of the patient's pain which correlate with the stated symptoms. While pain is subjective and some are more tolerant to chronic pain than others, an approach to pain management needs to be based on the body's ability to heal, as well as the pathophysiological understanding of its etiology. Our bodies usually heal rapidly from surgery and most forms of trauma.⁶

Opiate prescribing practices of individual physicians are being scrutinized. There is obvious over prescribing of opiates by some physicians and there are opiate-prescribing mills operating as legitimate pain management clinics. State and federal efforts are underway to close these prescription mills which are legalized drug-dealing businesses. In some cases, unscrupulous physicians are doing the same thing in their individual practices.

Continuing medical education training on analysis of chronic pain, pathophysiology, and severity are being provided to educate physicians on evidence based methods of treating chronic pain. The same approach needs to be applied to medical marijuana.

There is no current rationale to support that prescribing marijuana would be preferable to other approaches to pain management. Unfortunately, medical marijuana laws are passed as a means to bypass the illegality of marijuana. Medicine has often been an unwilling participant in this process.

Marijuana as an Addicting Drug

It is an erroneous belief widely held by the general public, and among many physicians, that marijuana is not addicting. Marijuana is a powerful mind-altering drug which impacts the addiction circuitry in the brain in a manner similar to all other mind-altering addicting drugs. ⁷⁻¹⁰ Our patients seeking help with marijuana addiction see it as an addicting drug that is harming their lives and they are unable to stop its use.

Marijuana addiction has been difficult to treat in our experience. Patients can experience lengthy periods of withdrawal and describe withdrawal symptoms that can continue for months after cessation of use. 7,10-15

Many have been using marijuana for decades and don't realize their degree of the dependence until they try to stop. Because their marijuana use played such an important part in maintaining homeostasis in their lives, a feeling of emptiness and alienation often accompanies cessation of the drug.

Researchers have found that non-addicted volunteers who were administered high-dose marijuana over a several week period demonstrated significant drug withdrawal symptoms on abrupt cessation of the drug. The symptoms show striking similarities to the general sedative-hypnotic withdrawal syndrome. They describe anxiety, agitation, tremulousness, elevation of vital signs, insomnia, and irritability as various components of marijuana withdrawal.^{13,15,16} These are similar withdrawal symptoms seen with any of the sedative-hypnotic drugs, including alcohol, benzodiazepines, barbiturates, and most hypnotic agents. While it is not typical to observe such severe withdrawal in usual marijuana subjects, the severity of marijuana withdrawal matches dosage, use pattern, and length of addiction.

By comparison, heavy alcohol users also may not experience severe withdrawal symptoms on cessation of the drug, but those who consume a liter of spirits per day or its equivalent in wine or beer can have severe withdrawal effects that include seizures and delirium tremens. Neither seizures nor delirium tremens have been described with marijuana withdrawal.

We might argue over why our nation has chosen to legitimize the use of alcohol, nicotine, and caffeine, despite their well-known detrimental effects. I suspect it is more likely due to long-term social mores and customs than on research on potentially harmful effects.

Nicotine addiction and the terrible consequences evidenced in the high death rate from cigarette smoking in the 20th century are well known and continue into the 21st century. The medical profession does not support or promote the heavy use of any legal or illegal drugs. Decriminalization and/or legalization of marijuana use is a state and federal issue. Legalization under the guise of medical necessity is wrong in my opinion and should

not be supported by the medical profession.

We don't have accurate studies on driving impairment caused by marijuana intoxication or chronic marijuana use. ¹⁷ Marijuana card users may feel that their driving ability is not impaired, but I doubt that they are accurate observers of their level of impairment. Nor are drivers impaired by alcohol.

Summary

Rigorous scientific research is needed before marijuana can be approved for the treatment of chronic pain or any other conditions. It would also be important for the government to remove marijuana from Schedule I to allow the research that would quickly follow. Until that research is done, stating that marijuana is useful for treating chronic pain, anxiety, post-traumatic stress disorder, depression, and other health conditions remains anecdotal and conjectural.

Anecdotal findings in medicine are not usually accepted, though they may serve as the basis for more extensive research on a topic. The randomized trials cited also refer to smoked marijuana. The number of "hits" to achieve pain relief is also described. How would legitimate research determine any effects based on "number of hits" of smoked marijuana? The research from those countries without scheduling problems: United Kingdom, Germany, Canada, Australia, other European and Latin American countries. ¹⁸⁻²⁴

Self-serving claims by medical marijuana users should not be used to base medically unsound conclusions.²⁵ If this is allowed, the medical profession loses creditability.

The national debate on marijuana as well as other drugs must continue so that we can all examine the basis for our laws, if we are to support any needed changes in them.

To date the "war on drugs" war has shown few visible results in stopping the promotion, distribution, or use of currently illegal drugs in the United States.

Our drug control laws show the fallacy of crafting legislation for a poorly understood national problem. We tolerate laws that made little sense 300 years ago, when attempts at legislating drug use began, and make no real sense from a social or medical perspective in our world today.²⁶

With appropriate changes in scheduling of banned drugs we may finally get answers to the legitimate question "What are the medical benefits of marijuana."

Conflict of Interest

The author does not identify any conflicts of interest.

Author's Biography:

Dr. McKenna graduated from Marist College in New York with a Bachelor of Arts degree in Biology in May 1962. He received his MD from the State University of New York — Upstate Health Sciences University, Syracuse, New York in May, 1966.

He completed a rotating internship at San Francisco General Hospital, University of California, from July 1, 1966, to June 30, 1967.

He completed a residency in Psychiatry at the Massachusetts Mental Health Center, Harvard Medical School, 1967 to 1970. He was a Chief Resident at the Cambridge Hospital Department of Psychiatry, at that time an integral part of the Massachusetts Mental Health Center, from 1969 to 1970.

Following two years in the United States Air Force as a captain from 1970 to 1971 as Chief of Psychiatry at the 11th US Air Force Hospital, U-Tapao, Thailand, and then

as a Major at the Pentagon, working with the Social Actions Assistance Team from August 1971 to August 1972.

He was on the faculty of Psychiatry at Harvard Medical School from 1972 to 1980 as an Instructor of Psychiatry. He was then on the faculty of the UCLA School of Medicine as an Adjunct Associate Professor of Psychiatry from 1980 to 1988. He was the Assistant Chief of Psychiatry at VAMC Brentwood from 1980 to 1984 and then Associate Chief of Psychiatry from 1984 to 1987.

He relocated to the island of Kaua'i where he has been in the practice of General Psychiatry and Addiction Medicine from March 1988 until the present time. He has held the academic rank of Associate Clinical Professor of Psychiatry at the John A. Burns School of Medicine, University of Hawai'i.

He has been the Medical Director of the McKenna Recovery Center, an outpatient addiction treatment program, from, 1989 to the present. He lives with his family on Kaua'i.

Author's Affiliation:

- McKenna Recovery Center, Ke Ala Pono - Kaua'i, Lihue, HI

Correspondence to:

Gerald J. McKenna MD; McKenna Recovery Center, Ke Ala Pono - Kaua'i, 4374 Kukui Grove St., Ste. 104;

Ph: (808)246-0663; Website: http://McKennaRecoveryCenter.com

- Szasz, T. Ceremonial Chemistry: The Ritual Persecution of Drugs, Addicts and Pushers. Garden City, NY: Anchor Press; 1974.
- U.S. Constitution. Amendment XVIII (repealed 1933); 1920.
- 3. U.S. Constitution. Amendment XXI; 1933.
- Food and Drug Administration. Controlled Substances Act. http://www.fda.gov/regulatoryinformation/legislation/ucm148726.htm. Accessed January 23, 2014.
- CNN. Study. 7.3 million in U.S. prison system in '07 [published March 2, 2009]. http://www.cnn.com/2009/CRIME/03/02/record.prison.population/. Accessed January 24, 2013.
- Bolla KI, Eldrett DA, Matochik JA, Codet JL. Neural substrates of faulty decision-making in abstinent marijuana users. Neuroimage. 2005 June;20(2):480-92.
- Havey M, Ward AS, Coner SD, Foltin RW, Fishman MW. Abstinence symptoms following oral THC administration to humans. Psychopharmacology (Berl). 1992 Feb;141(4):385-94.
- Allsop DJ, Copeland J, Norberg MM, et al. Quantifying the clinical significance of cannabis withdrawal. PLoS One. 2012; 7(9): e44864. doi: 10.1371-journal.pone.0044864. Epub 2012 Sep 26.
- Van Dam NT, Bedi G, Earleywine M. Characteristics of clinically anxious versus non-anxious regular, heavy marijuana users. Addict Behav. 2012 Nov;37(11):1217-23. doi:1.1016-j.addbeh.2012.05.021. Epub 2012 Jun 7.

- Tsao JC, Stein JA, Ostrow D, Stall RD, Plankey MW. The mediating role of pain in substance use and depressive symptoms among Multicenter AIDS Cohort Study (MACS) participants. *Pain*. 2011 Dec; 152(12):2757-64. doi:10.1016/j.pain.2011.08.024. Epub 2011 Oct 1.
- Muramatsu RS, Silva N, Ahmed I. Suspected dronabinol withdrawal in an elderly cannabis-naive medicallly itt patient. Am J Psychiatry. 2013 July 1;170(7): 804. doi:1.1176/appi. ajp.213.1301059.
- Rovai L, Maremmani AG, Pacini M, et al. Negative dimension in psychiatry. Amotivational syndrome as a paradigm of negative symptoms in substance abuse. Riv Psychiatr. 2013 Jan-Feb:48(1):1-9. doi:10.178-1228.13610.
- Roten AT, Baker NL, Gray KM. Marijuana craving trajectories in an adolescent marijuana cessation pharmacotherapy trial. Addict Behav. 2013 Mar;38(3):1788-91. doi:10.1016-j.addbeh.2012.11.004. Epub 2013 Nov 16.
- Boggs DL, Kelly DL, Liu F, et al. Cannabis withdrawal in chronic cannabis users with schizophrenia. J Psychiatr Res. 2013 Feb;47(2):240-5. doi: 10.1016/j.jpsychires.2013.10.010. Epub 2012 Nov 10.
- Wade D. Evaluation of the safety and tolerability profile of Sativex: is it reassuring enough? Expert Rev Neurother. 2012 Apr; 12(4 Suppl):9-14. doi:10.1586/ern.12.12.
- Wikler A. Aspects of tolerance to and dependence on cannabis. Am NYAcad Sci. 1976;282:126-147
- Sanches RF, Marques JM. Cannabis and mood. Rev Bras Psiquiatr. 2010;32:173–80. doi:10.1590/ S1516-4446201000200014.
- Nicholson SE, Denysenko L, Mulcare JL, Vito JP, Chabon B. Cannabinoid hyperemesis syndrome: a case series and review of previous reports. *Psychosomatics*. 2012 May-Jun;53(3):212-9. doi:10.1016-j.psym.2012.01.003. Epub 2012 Apr 4.
- Rosenbaum CD, Carreiro SP, Babu KM. Here today, gone tomorrow...and back again? A review
 of herbal marijuana alternatives: K2, spice, synthetic cathinones (bath salts), kratom, Salvia,
 divinorum, methoxetamine, and piperazines. *J Med Toxicol*. 2012 Mar; 8(1):15-32. doi:10.1007/s13181-011-0202-2.
- Ware MA. Clearing the smoke around medical marijuana. Clin Pharmacol Ther. 2011 Dec;90(6):769-71. doi:10.1038-clpt.2011.241.
- Heltsley R, DePriest A, Black DL, et al. Oral fluid drug testing of chronic pain patients. I. Positive prevalence rates of licit and illicit drugs. J Anal Toxicol. 2011 Oct;35(8):529-40.
- Zvolensky MJ, Cougle JR, Bonn-Miller MO, et al. Chronic pain and marijuana use among a nationally representative sample of adults. Am J Addict. 2011 Nov-Dec;20(6):538-42. doi:10.1111/j.1521-0391.2011.00176.x.
- Nussbaum A, Thurstone C, Binswanger I. Medical marijuana use and suicide attempt in a patient with major depressive disorder. Am J Psychiatry. 2011 Aug; 168(8): 778-81. doi: 10.1176/appi. ajp.2011.10121769.
- Price SL, Fisher C, Kumar, Hilgerson A. Cannabinoid hyperemesis syndrome as the underlying cause of intractable nausea and vomiting. J Am Osteopath Assoc. 2011 Mar;111(3):166-9.
- Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials. Br J Clin Pharmacol. 2011 Nov;72(5);735-44. doi: 10.1111/j.1365-2125.2011.03970.x.
- Elgen, Bohrest, Kleinberg, et al. Characteristics of patients seeking treatment with the use of medical marijuana. Drug and alcohol dependence. 132(3):654-659.

Therapeutic Benefits of Cannabis: A Patient Survey

Charles W. Webb MD and Sandra M. Webb RN. BSN

Abstract

Clinical research regarding the therapeutic benefits of cannabis ("marijuana") has been almost non-existent in the United States since cannabis was given Schedule I status in the Controlled Substances Act of 1970. In order to discover the benefits and adverse effects perceived by medical cannabis patients, especially with regards to chronic pain, we hand-delivered surveys to one hundred consecutive patients who were returning for yearly re-certification for medical cannabis use in Hawai'i.

The response rate was 94%. Mean and median ages were 49.3 and 51 years respectively. Ninety-seven per cent of respondents used cannabis primarily for chronic pain. Average pain improvement on a 0-10 pain scale was 5.0 (from 7.8 to 2.8), which translates to a 64% relative decrease in average pain. Half of all respondents also noted relief from stress/anxiety, and nearly half (45%) reported relief from insomnia. Most patients (71%) reported no adverse effects, while 6% reported a cough or throat irritation and 5% feared arrest even though medical cannabis is legal in Hawai'i. No serious adverse effects were reported.

These results suggest that Cannabis is an extremely safe and effective medication for many chronic pain patients. Cannabis appears to alleviate pain, insomnia, and may be helpful in relieving anxiety. Cannabis has shown extreme promise in the treatment of numerous medical problems and deserves to be released from the current Schedule I federal prohibition against research and prescription.

Introduction

Research into the therapeutic benefits of cannabis has been severely limited by the federal Schedule I classification, which essentially prohibits any ability to acquire or to provide cannabis for studies investigating possible therapeutic effects. Limited studies have been done in Canada and in Europe, as well as several in California.

Hawai'i is one of twenty states (plus the District of Columbia) which allow certifications for use of medical cannabis. The authors have been certifying patients for use of medical cannabis in Hawai'i for more than four years. In an attempt to discover the perceived benefits and adverse effects of medical cannabis, we conducted a survey of medical cannabis patients.

Methods

Sample Selection

Between July of 2010 and February of 2011, we hand-delivered questionnaires to one hundred consecutive patients who had been certified for the medical use of cannabis for a minimum of one year and were currently re-applying for certification.

Survey Design and Administration

The subjects were verbally instructed to complete the questionnaire in the office at the time of re-certification or were provided a stamped and addressed envelope so they could complete the questionnaire at home. All patients were instructed to remain anonymous and to answer the questions as honestly as possible.

A universal pain scale was used to assess pain before and after treatment (0 = no pain, 10 = worst pain ever). Open-ended questions were asked to ascertain the following:

- (1) "Any adverse effects you have had from using medical cannabis?"
- (2) "Does medical cannabis help you with any other problems? If so, what?"

The purpose of the last question was to explore benefits outside the parameters of the state of Hawai'i's medical cannabis qualifying conditions.

Results

The overall response rate was 94%. The mean age was 49.3 years and the median age was 51. No data was collected on sex or race/ethnicity. Almost all respondents (97%) used medical cannabis primarily for relief of chronic pain.

Average reported pain relief from medical cannabis was substantial. Average pre-treatment pain on a zero to ten scale was 7.8, whereas average post-treatment pain was 2.8, giving a reported average improvement of 5 points. This translates to a 64% average relative decrease in pain.

Other reported therapeutic benefits included relief from stress/anxiety (50% of respondents), relief of insomnia (45%), improved appetite (12%), decreased nausea (10%), increased focus/concentration (9%), and relief from depression (7%). Several patients wrote notes (see below) relating that cannabis helped them to decrease or discontinue medications for pain, anxiety, and insomnia. Other reported benefits did not extend to 5% or more of respondents.

Six patients (6%) wrote brief notes relating how cannabis helped them to decrease or to discontinue other medications. Comments included the following: "Medical cannabis replaced my need for oxycodone. Now I don't need them at all." "I do not need Xanax anymore." "In the last two years I have been able to drop meds for anxiety, sleep, and depression." "I've cut back 18 pills on my morphine dosage."

A majority (71%) reported no adverse effects, while 6% reported a cough and/or throat irritation and 5% reported a fear of arrest. All other adverse effects were less than 5%. No serious adverse effects were reported.

Discussion

According to the Institute of Medicine, chronic pain afflicts 116 million Americans and costs the nation over \$600 billion every year in medical treatment and lost productivity. Chronic pain is a devastating disease that frequently leads to major depression and even suicide. Unfortunately, the therapeutic options for chronic pain are limited and extremely risky.

Spurred by efforts to encourage physicians to become more pro-active in treating chronic pain, US prescription opioids (synthetic derivatives of opium) have increased ten-fold since 1990.³ By 2009 prescription opioids were responsible for almost half a million emergency department visits per year.⁴ In 2010 prescription opioid overdoses were responsible for well over 16,000 deaths.⁵ A 2010 article in the *New England Journal of Medicine* addressing this problem is aptly titled "A Flood of Opioids, a Rising Tide of Deaths." Drugs such as OxyContin^R are so dangerous that the manufacturer's boxed warning states that "respiratory depression, including fatal cases, may occur with use of OxyContin, even when the drug has been used as recommended and not misused or abused." Clearly safer analgesics are needed.

The Hippocratic Oath reminds to "first, do no harm." It cannot be over-emphasized that there has never been a death from overdose attributed to cannabis. In fact, no deaths whatsoever have been attributed to the direct effects of cannabis. Cannabis has a safety record that is vastly superior to all other pain medications.

Many physicians worry that cannabis smoke might be as dangerous as cigarette smoke; however, epidemiologic studies have found no increase in oropharyngeal or pulmonary malignancies attributable to marijuana. Still, since smoke is something best avoided, medical cannabis patients are encouraged to use smokeless vaporizers which can be purchased on-line or at local "smoke-shops." In states that (unlike Hawai'i) allow cannabis dispensaries, patients can purchase "vapor pens," analogous to e-cigarettes and fully labeled regarding doses of THC and other relevant cannabinoids.

Tests have proven that smoke-free vaporizers deliver THC as well or even more efficiently than smoking, and that most patients prefer vaporizers over smoking. ¹¹Like smoking, vaporizers allow patients to slowly titrate their medicine just to effect, analogous to IV patient-controlled analgesia (PCA) that has been so successful in hospital-based pain control. This avoids the unwanted psychoactive side-effects often associated with oral medication such as prescription Marinol^R (100% THC in oil) capsules which tend to be slowly and erratically absorbed and are often either ineffectually weak or overpoweringly strong. ^{12,13} Because inhaled cannabis is rapid, reliable, and titratable, most patients strongly prefer inhaled cannabis over Marinol^R capsules. ¹⁴

While the relative safety of cannabis as medication is easily established, the degree of efficacy is still being established. The reported pain relief by patients in this survey is enormous. One reason for this is that patients were already self-selected for success: they had already tried cannabis and found that it worked for them. For this sample, the benefits of cannabis outweighed any negative effects. The study design may therefore lend itself to over-estimating the benefits and under-estimating the negative side-effects if extrapolated to the general population.

Another reason that the reported pain relief is so significant is that cannabis has been proven effective for many forms of recalcitrant chronic pain. A University of Toronto systematic review of randomized controlled trials (RCT's) examining cannabinoids in the treatment of chronic pain found that fifteen of eighteen trials demonstrated significant analgesic effect of cannabinoids and that there were no serious adverse effects.¹⁵

While opioids are generally considered to have little benefit in chronic neuropathic pain, several RCT's have shown that cannabinoids can relieve general neuropathic pain, ¹⁶ as well as neuropathic pain associated with HIV and with multiple sclerosis (MS). ^{17,18} One study found that cannabis had continuing efficacy at the same dose for at least two years. ¹⁹

Even low dose inhaled cannabis has been proven to reduce neuropathic pain. In a randomized, double-blind, placebo-controlled crossover trial involving patients with refractory neuropathic pain, Ware, et al, found that therapeutic blood levels of THC (mean 45 ng/ml achieved by a single inhalation three times a day) were much lower than those necessary to produce a cannabis euphoria or "high" (> 100 ng/ml). 19

Cannabis is relatively non-addicting, and patients who stop using it (eg, while traveling) report no withdrawal symptoms. One author (Webb C.) worked for 26 years in a high volume emergency department where he never witnessed a single visit for cannabis withdrawal symptoms, whereas dramatic symptoms from alcohol, benzodiazepine, and/or opioid withdrawal were a daily occurrence.

So why is cannabis still held hostage by the DEA as a Schedule I substance? On June 18,2010, the Hawai'i Medical Association passed a resolution stating in part that:

"Whereas, 1) Cannabis has little or no known withdrawal syndrome and is therefore considered to be minimally or non-addicting; and

Whereas, 2) Cannabis has many well-known medical benefits (including efficacy for anorexia, nausea, vomiting, pain, muscle spasms, and glaucoma) and is currently recommended by thousands of physicians; and

Whereas 3) Cannabis has been used by millions of people for many centuries with no history of recorded fatalities and with no lethal dosage ever discovered; and

Whereas, Cannabis therefore fulfills none of the required three criteria (all of which are required) to maintain its current restriction as a Schedule I substance...

The Hawai'i Medical Association recommends that Medical Cannabis be re-scheduled to a status that is either equal to or less restrictive than the Schedule III status of synthetic THC (Marinol^R), so as to reduce barriers to needed research and to humanely increase availability of cannabinoid medications to patients who may benefit."²⁰

Medical cannabis remains controversial mainly because the federal government refuses to recognize cannabis as an accepted medication. To this we would echo the words of Melanie Thernstrom in her excellent book *The Pain Chronicles*,² "How could treating pain be controversial?" one might ask, "Why wouldn't it be treated? Who are the opponents of relief?"

Conclusions

Cannabis is an extremely safe and effective medication for many patients with chronic pain. In stark contrast to opioids and other available pain medications, cannabis is relatively non-addicting and has the best safety record of any known pain medication (no deaths attributed to overdose or direct effects of medication). Adverse reactions are mild and can be avoided by titration of dosage using smokeless vaporizers.

More research needs to be pursued to discover degrees of efficacy in other areas of promise such as in treating anxiety, depression, bipolar disorder, autism, nausea, vomiting, muscle spasms, seizures, and many neurologic disorders. Patients deserve to have cannabis released from its current federal prohibition so that scientific research can proceed and so that physicians can prescribe cannabis with the same freedom accorded any other safe and effective medications.

Conflict of Interest

None of the authors identify a conflict of interest.

Authors' Biography:

Dr. Webb graduated from Dartmouth Medical School (BS Medicine) and from UC San Francisco School of Medicine (MD 1974). General Residency US Public Health Hospital (San Francisco) and Highland Hospital (Oakland). Emergency Medicine Physician 1975-2006 (Colorado), Urgent Care Physician 2007-present (Kailua Kona). Sandra Webb RN, since 1979 (emergency and radiology nurse). Dr. Webb and nurse Webb have been certifying patients for medical use of cannabis since 2009.

Authors' Affiliation:

- Keauhou Urgent Care Center, 78-6831 Alii Dr., Suite 418, Kailua Kona, HI 96740

Correspondence to:

Charles W. Webb MD; 73-993 Ahikawa St, Kailua Kona, HI 96740; Email: forecharlee@msn.com

- . Institute of Medicine of the National Academy. Relieving Pain in America. 2011.
- 2. Thernstrom M. The Pain Chronicles. New York: Farrar, Straus and Giroux; 2011
- 3. Oakie S. A Flood of Opioids, a Rising Tide of Death. NEJM. 2010;363:1981-1985.
- Substance Abuse and Mental Health Services Admin. Drug Abuse Warning Network: selected tables of national estimates of drug-related emergency visits. Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA; 2010.
- CDC. Opioids Drive Continued Increase in Drug Overdose Deaths. Press release Feb 20, 2013.
- Purdue Pharma LP. An Overview of the Oxycontin Label Update Deterrence Studies. 07/13.
 Iverson LL. The Science of Marijuana. New York: Oxford University Press; 2000.
- Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GC. Marijuana use and mortality. Am J Public Health. 1997: 87(4):585-590.
- Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF. Epidemiologic review of marijuana use and cancer risk. Alcohol. 2005;35(3):265-275.
- 10. Tashkin DP. Smoked marijuana as a cause of lung injury. *Monaldi. Arch Chest Dis.* 2005;63(2):93-
- Abrams D, et al. Vaporization as a Smokeless Cannabis Delivery System. Clin. Pharmacol. Ther. 2007;82(5):572-578.
- 12. nstitute of Medicine. Marijuana and Medicine: Assessing the Science Base. 1999.
- Weil A. San Francisco Chronicle. June 6, 2002.
- Grinspoon L. "I have yet to examine a patient who has used both smoked marijuana and Marinol who finds the latter more useful." *International Journal of Drug Policy*. 2001 Issue.
- Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systemic review of randomized trials. Br, J. Clin Pharmacol. 2011 Nov; 72(5):735-44.
- Wilsey B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9(6):506-521.
- Abrams D, et al. Cannabis in Painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007; 68(7):515-521.
- Rog, et al. Oromucosal THC/cannabidiol for neuropathic pain associated with MS. Clin Ther. 2007;29(9):2068-2079.
- Ware MA, Ducruet T, Robinson AR. Evaluation of herbal cannabis characteristics by medical users: a randomized trial. Harm Reduction J. 2006 Nov 13;3:32.
- 20. Hawai'i Medical Association Resolution, June 18, 2010.

Paraneoplastic Syndrome in Hawai'i: A Case of Dermatomyositis Associated with Endometrial Cancer

Cherisse Wada MSIII; Charles N.C. Hua MS, MSIII; and Michael E. Carney MD

Abstract

Dermatomyositis as a paraneoplastic consequence of gynecological malignancy has rarely been reported in literature and never been reported in Honolulu. This case report describes a local Honolulu resident who was diagnosed with endometrial adenocarcinoma upon presenting with acute dermatomyositis symptoms.

Keywords

Paraneoplastic, gynecological, gynecology, endometrial, ovarian, adenocarcinoma, cancer, local, dermatomyositis, myositis, Gottron papules, heliotrope erythema

Introduction

Adult-onset classic dermatomyositis is a rare type of inflammatory myopathy associated with an increased incidence of malignancy. There have been reports linking paraneoplastic dermatomyositis with female reproductive tract cancers, with ovarian adenocarcinoma being the most common. However, an association with endometrial carcinoma—the most common cancer of the female reproductive organs in the United States—is rare. In this report, we discuss and describe a case of paraneoplastic syndrome as a consequence of endometrial adenocarcinoma occurring in Honolulu in 2013.

Case Report

The case report herein describes a nulliparous 46-year-old local professional woman who presented to her dermatologist for a skin rash on her hands and chest lasting three months, which had appeared suddenly after a marathon race and persisted. Although creatinine phosphokinase levels were not assessed, a skin biopsy was performed and the patient was subsequently diagnosed with dermatomyositis. Further work up to screen for internal malignancy was performed, and computerized tomographic scans of the chest, abdomen and pelvis revealed an intrauterine mass. She was then referred to gynecology and the gynecologic oncology service at a local clinic for consult.

The patient denied any significant past medical history including hypertension, diabetes, or polycystic ovarian syndrome. Her gynecologic history was unremarkable; menarche occurred at age 13 and she denied any sexually transmitted infections or abnormal pap smears. She previously took drospirenone contraceptive for 2 years but stopped recently. She denied smoking or using recreational drugs, and reported drinking alcohol on rare occasions. She was physically active and exercised regularly.

On exam, the patient had an athletic build, with a height of 156 cm (5'2"), weight of 47.6 kg (105 lbs), and vital signs: blood pressure 140/91 mm Hg; pulse 100; respiratory rate 18; and temperature 37.3 °C (99.2 °F). Physical exam revealed characteristic heliotrope rash, Gottron papules on her hands

and scattered erythema on her chest, with no signs of androgen excess such as obesity, hirsutism, acne, or male pattern baldness. Pelvic exam revealed a small amount of dark blood in the vaginal vault with no discharge, lesions, rashes, or masses on external structures, vagina, or cervix. The uterus was mobile and nontender, and appeared of normal size. There was no evidence of right adnexa masses; however, there was a large, nontender, firm, left adnexal mass. Rectovaginal exam was within normal limits. Labs revealed microcytic anemia with a hemoglobin of 8.1 g/dL.

Transvaginal ultrasonographic exam showed an irregularly shaped,homogenous,highly vascular,intracavitary lower uterine mass measuring $3.3 \times 2.6 \times 3.2$ cm and a suboptimally visualized,highly vascular,intracavitary upper uterine mass measuring $1.0 \times 1.2 \times 1.1$ cm. There was also a large left ovarian complex cystic/solid mass with marked vascularity measuring $7.94 \times 4.57 \times 5.99$ cm, which replaced the entire left ovary. Dilation and endometrial curettage revealed grade 2-endometrioid-type 1 endometrial adenocarcinoma.

A robotic total hysterectomy and bilateral salpingo-oophorectomy with paraaortic sentinel node biopsy were performed. On inspection, there was no obvious peritoneal carcinomatosis. The uterus appeared 8 weeks in size and there was a 10-week size left ovarian mass, which was densely adherent to the left pelvic sidewall and infiltrating through the parapelvic sidewall and into the parametria. Frozen section of one enlarged lymph node obtained on the left was negative for metastatic disease; however, histological exam confirmed grade 2-endometrioidtype 1-endometrial adenocarcinoma with metastasis to right and left ovaries without lymph node involvement, consistent with the International Federation of Gynecology and Obstetrics (FIGO) Stage IIIB. Pelvic washings were negative for malignancy. She attended follow up every three weeks for five months, and received six cycles of carboplatin with an AUC (area under curve) of 6 mg/mL min and paclitaxel 175 mg/m² every three weeks. Her skin condition gradually improved over this time period.

Discussion

Endometrial cancer is the most common gynecological malignancy in the United States, with an estimated 40,000 new cases annually.^{4,5} Risk factors are associated with increasing age, diabetes mellitus, family history (hereditary nonpolyposis colorectal cancer), and excessive estrogen states: obesity, early menarche, late menopause, nulliparity, polycystic ovarian syndrome, unopposed estrogen therapy, and tamoxifen therapy.⁶ The most common symptom is postmenopausal bleeding and diagnosis is confirmed with endometrial biopsy or dilation

and curettage. 46 Patients diagnosed with endometrial cancer should undergo hysterectomy, bilateral salpingoophrectomy, pelvic washings and surgical staging with pelvic and paraaortic lymphadenectomy as per the revised FIGO system. 7 According to the American College of Gynecologists (ACOG), most surgically treated patients can be followed with pelvic examinations every 3-4 months for the first two years, and then twice yearly for an additional three years before returning to annual visits. Paclitaxel, doxorubicin, and cisplatin chemotherapy is the adjuvant treatment of choice for advanced endometrial cancer following surgery. 6

Adult-onset classic dermatomyositis was originally proposed by Stertz in 1916 as a paraneoplastic syndrome associated with malignancy. Since then, numerous case reports have demonstrated that it is more common in female patients over 50 years of age and in association with ovarian, lung, pancreatic, stomach, and colon cancers, as well as non-Hodgkin lymphomas. Ovarian cancer appears to have the highest association with dermatomyositis, and the association of dermatomyositis with other gynecologic malignancies such as endometrial cancer is relatively rare. 9,10

The pathogenesis of dermatomyositis in malignancy is poorly understood, but is thought to be caused by altered cellular and humoral immunity. According to Casciola-Rosen, et al, myositis-specific autoantigen, histadyl tRNA synthetase (HRS/Jo-1) are expressed at higher levels in myositis muscles, regenerating muscle cells, lung and breast cancer, and hepatocellular carcinoma, suggesting that there may be cross-reactivity of autoantigens against cancer cells with regenerating muscle cells. 12

Clinical manifestations range from cutaneous inflammation to polymyositis. However, cutaneous involvement is common and includes photosensitivity, periorbital heliotrope rash, Gottron's papules, poikiloderma (triad of atrophy, dyspigmentation, and telangiectasia), and periungal telangiectasia. Although these findings are less likely to be associated with muscle abnormalities, 2.13,14 the risk for malignancy is highest within one year of diagnosing myositis. 2

Diagnosis of dermatomyositis—which usually occurs two years before or after the diagnosis of malignancy—is based on characteristic skin lesions and laboratory findings such as increased creatinine phosphokinase, aldolase, and lactate dehydrogenase. Definitive diagnosis may be made by either a skin biopsy or muscle biopsy. However, no diagnostic criteria exists to establish dermatomyositis as a paraneoplastic consequence of malignancy; the anti-p155 autoantibody may be useful in diagnosing cancer-associated myositis and guiding disease management. If that a specificity of 89%, sensitivity of 70% and a negative predictive value of 93%.

A thorough history and physical exam—including a rectal exam, and breast and pelvic exam in women or testicular exam in men—should be performed in all patients newly diagnosed with dermatomyositis. Additional studies such as a colonoscopy, and mammogram and pap smear in women or prostate specific

antigen in men, should also be done. ¹⁸ The patient should be followed with gynecologic examinations every 6-12 months for the first three years, or five years for ovarian cancer, after the diagnosis of dermatomyositis. ^{7,13}

Treatment for non-paraneoplastic dermatomyositis is managed with high dose corticosteroid and tapered when muscle enzymes begin to normalize.¹³ However, malignancy related dermatomyositis is much less responsive to systemic glucocorticoid therapy and definitive treatment of the underlying malignancy usually results in symptom regression.^{19,20}

Conclusion

Adult-onset classic dermatomyositis is associated with gynecologic malignancies and usually presents prior to the onset of malignancy. Physicians should be aware of this association so that these patients may be appropriately managed, allowing for early clinical evaluation of malignancy and improved patient outcomes.¹⁹

Conflict of Interest

None of the authors identify a conflict of interest.

Authors' Affiliation

- John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI

Correspondence to:

Michael E. Carney MD; 1319 Punahou St., Suite 640, Honolulu, HI 96826; Ph: (808) 203-6530; Email: mcarney@hawaii.edu

- Jones G, Razdan D, Cracchiolo B, Houck K & Sharer L. Paraneoplastic SIADH and Dermatomyositis in Cervical Cancer: A Case Report and Literature Review. Case Rep Oncol. 2009;2:203-9.
- Hill CL, Zhang Y, Sigurgeirsson B, Pukkula E, Mellemkjaer L, Airio A, Evans SR, Felson DT. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet*. 2001;357:96-100.
- Reichert S, Barbaud A, Tagu P, Conroy T & Schmutz JL. Double paraneoplastic syndrome in a case of adenocarcinoma of the endometrium associated with Sezary syndrome (letter). Presse Med. 1993;22:1368-9.
- Crum CP, Nucci MR & Lee KR. Diagnostic Gynecologic and Obstetric Pathology, 2nd ed. 2011. Philadelphia: Elsevier.
- Hoffman B, Schorge J, Schaffer, J, Halvorson L, Bradshaw K, Cunningham F. Williams Gynecology, 2nd ed. New York: McGraw-Hill; 2012.
- Wright JD, Mendel NIB, Sehouli J, Fujiwara K & Herzog T. Contemporary management of endometrial cancer. The Lancet. 2012;379:1352-60.
- American College of Obstetricians and Gynecologists (ACOG). Management of endometrial cancer. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2005: ACOG practice bulletin; no. 65).
- Przybylski G, Jarzemaska A, Czerniak, J, Siemiatkowska, K, Gadzińska A & Cieśliński K. A
 case report of a patient with dermatomyositis as a prodromal sign of lung cancer. Pol Arch Med
 Wewn. 2008;118:143-7.
- Barnes BE, Mawr B. Dermatomyositis and malignancy. A review of the literature. Ann Intern Med. 1976;84:68-76.
- Levine D, Miller S, Al-Dawsari N, Barak O, Gottlieb AB. Paraneoplastic dermatoses associated with gynecologic and breast malignancies. Obstet Gynecol Surv. 2010;65:455-61.
- Buchbinder R, Hill CL. Malignancy in patients with inflammatory myopathy. Curr Rheumatol Rep. 2002;4:415-26.
- Casciola-Rosen L, Nagaraju K, Plotz P, Wang K, Levine S, Gabrielson E, Corse A, Rosen A. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. J Exp Med. 2005;201:591-601.
- Wolff K, Johnson R. Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology. 6th ed. New York: McGraw-Hill; 2009.
- Ghazi E, Sontheimer RD, Werth VP. The importance of including amyopathic dermatomyositis in the idiopathic inflammatory myositis spectrum. Clin Exp Rheumatol. 2013;31:128-34.
- Higgens ÉM, Du Vivier AW. Cutaneous manifestations of malignant disease. Br J Hosp Med. 1992;48:552-4, 558-61.
- Cai Y, Qiao J, Fang H. Metachronous multiple primary malignant neoplasms in a patient with dermatomyositis. *Indian J Dermatol Venereol Leprol*. 2012;78:665.

- Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O'Callaghan A, Martínez-Gómez X, Bosch X, Labrador-Horrillo M, Grau-Junyent JM, Vilardell-Tarrés M. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: A systematic review and meta-analysis. Arthritis Rheum. 2012;64:523-32.
 Marvi U, Chung L & Fiorentino DF. Clinical Presentation and Evaluation of Dermatomyositis. Indian J Dermatol. 2012;57:375-81.
- Verducci MA, Malkasian GD Jr, Friedman SJ, Winkelmann RK. Gynecologic carcinoma associated with dermatomyositis-polymyositis. *Obstet Gynecol.* 1984;64:695-8.
 Orth T, Galle PR, Vayet WJ. Severe dermatomyositis associated with lymph node recurrence of an endometrial carcinoma. *J Clin Rheumatol.* 1999;5:41-2.

Mid-ventricular Variant Takotsubo Cardiomyopathy Associated with Cannabinoid Hyperemesis Syndrome: A Case Report

Masayuki Nogi MD; David Fergusson MD; and John Michael Chua Chiaco MD

Abstract

A case of the mid-ventricular variant of takotsubo cardiomyopathy is reported, occurring in a patient with Cannabinoid Hyperemesis Syndrome (CHS), and presented with a review of the relevant literature. The patient is a 32-yearold woman who presented with epigastric pain, nausea and vomiting. Her EKG showed dynamic T-wave changes associated with a modest cardiac biomarker elevation. Ventricular wall motion abnormalities suggestive of the mid-ventricular variant of takotsubo cardiomyopathy were demonstrated by echocardiography, ventriculography and cardiac angiography, the latter showing normal coronary arteries. The patient was a previous marijuana user who had recently ingested marijuana after a period of abstinence. Severe epigastric pain, nausea and cyclic vomiting followed this. She had previously experienced similar gastrointestinal symptoms, relieved by compulsive hot water bathing, and resolving after marijuana cessation. Recent resumption of marijuana use was followed by a recurrence of these symptoms, a pattern characteristic of CHS. The association of cardiomyopathy with CHS has been described only once in the literature, and if this is a true relationship, its mechanism is not clearly defined. Animal models have suggested that endocannabinoid receptors are expressed in the myocardium, which could be a pathway for developing cardiac manifestations with cannabinoid use.

Keywords

cannabinoid hyperemesis, CB-1, takotsubo cardiomyopathy, marijuana

Introduction

Marijuana use is common worldwide, and Hawai'i is no exception. Nationwide data reveals significant rise in usage. According to the 2012 National Survey of Drug Use and Health (NSDUH) data, 5.4 million persons aged 12 or older used marijuana on a daily or almost daily basis in the past 12 months. In Hawai'i, 2010-2011 state specific data from the same source report 11.86% of residents over 12 years old used marijuana in the year 2009.

Δ9-tetrahydrocannabinol (THC) is the active ingredient of the marijuana plant *Cannabis sativa*. Several synthetic analogues are now available that mimic the action of THC. Cannabinoids stimulate endogenous Cannabinoid-1 (CB-1) and Cannabinoid-2 (CB-2) receptors. These receptors are located in the central nervous system, on the dorsal ganglia, hypothalamus, hippocampus, and cerebellum, and also on the peripheral enteric nerves and the presynaptic ganglia of the parasympathetic system.²

Observational studies have reported the gastrointestinal effect of cannabinoids, but little is known about cardiac involvement. Cannabinoid Hyperemesis Syndrome (CHS) is characterized by a striking pattern of cyclic nausea and vomiting among long-term marijuana users with relief from compulsive hot water bathing.³⁻⁷ The nausea and vomiting appear somewhat paradoxical, given the effectiveness of marijuana as a palliative antiemetic agent in cancer patients. The exact mechanism is still unknown, but it is hypothesized that impaired physiological thermoregulation provoked by long-term cannabinoid usage may account for the

Table 1. Proposed Clinical Criteria for Cannabinoid Hyperemesis

Essential for diagnosis - Long term cannabis use

Major features - 1) Severe cyclic nausea and vomiting. 2) Resolution with cannabis cessation. 3) Relief of symptoms with hot showers or baths. 4) Abdominal pain, epigastric or periumbilical. 5) Weekly use of marijuana

Supportive features – 1) Age less than 50 years old. 2) Weight loss of > 5kg. 3) Morning predominance of symptoms. 4) Normal bowel habits. 5) Negative laboratory, radiographic and endoscopic test results

Derived from Simonetto, et al.6

symptom relief by hot water bathing.^{6,8-10} The pathophysiology of CHS is not well understood. Proposed components of the mechanisms have included the following: first, central effects of long-term cannabis use on the hypothalamic-pituitary-adrenal axis; and, second, dysregulation of peripheral enteric nerves causing delayed gastric emptying and abdominal pain.^{3,4,6,7}

Since the first case series of CHS reported by Allen, et al, in 2004, there have been a few more small case series reports of CHS in the literature. ^{8,9,11,12} In 2012, Simonetto, et al, reviewed 98 patients with CHS and modified the previously proposed clinical criteria for diagnosing CHS (Table1); the study improved our understanding of this under-recognized syndrome, but despite being the largest case series on CHS to date, cardiac complications were not reported. ^{6,9,13} The authors are aware of only one previous case report of cannabis-associated cardiomyopathy. In 2011, Kaushik, et al, reported a case of a chronic cannabinoid user presenting with recurrent stress cardiomyopathy with variable regional involvement. ^{11,12,14,15} The study proposed a CB1-mediated cardiovascular effect to potentially explain this association. This is a case report of mid-ventricular variant takotsubo cardiomyopathy associated with CHS.

Case Description

A 32-year-old Puerto Rican woman with a history of hypertension, dyslipidemia, migraine headaches, and prior marijuana use, presented with seemingly unprovoked epigastric pain associated with nausea, vomiting, diaphoresis, and non-bloody emesis beginning on the day prior to admission. She had been experiencing similar symptoms intermittently over the previous year, prompting upper gastrointestinal endoscopy which was unremarkable except for an incidental hiatal hernia. Except for mild epigastric tenderness, her physical exam was normal. Liver function tests, serum amylase, and serum lipase were normal. Abdominal ultrasound was normal. Non-contrast chest, abdominal, and pelvic CT were normal except for a non-obstructing 3mm right renal calculus.

The patient's EKG initially showed minor STT abnormalities with progression to anterolateral T-wave inversion (Figure 1).

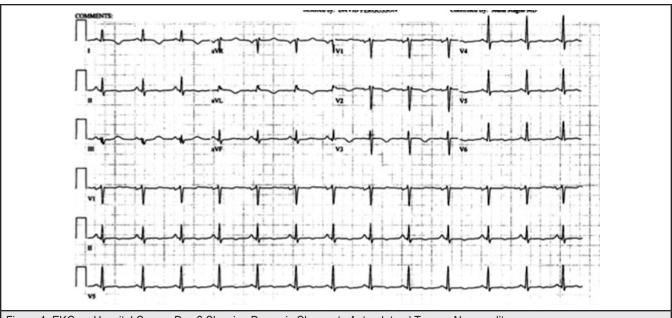


Figure 1. EKG on Hospital Course Day 2 Showing Dynamic Change to Anterolateral T-wave Abnormality

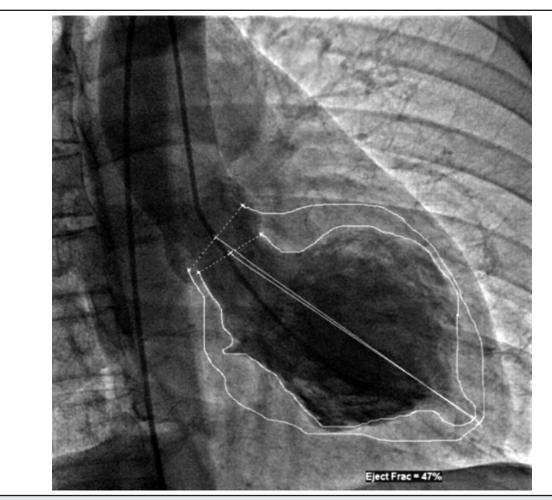


Figure 2. Ventriculogram Showing Severe Mid-ventricular Hypokinesis with Preservation of Apical and Basal Function

Troponin-I (reference <0.05ng/mL) rose from 0.96 ng/mL to a peak level of 1.93 ng/mL. Creatinine kinase – muscle and brain subunit (CK-MB) (reference <3.8ng/mL) was 8.1 ng/mL, and subsequently decreased. B type natriuretic peptide (reference <100pg/mL) was 1167pg/mL. Transthoracic echocardiography demonstrated a left ventricular ejection fraction of 30-35% with severe mid-ventricular hypokinesis and preservation of apical and basal function. Cardiac ventriculography (Figure 2) showed an appearance similar to that on the echocardiogram, and the coronary arteries were normal. A diagnosis of the midventricular variant of takotsubo cardiomyopathy was made.

During bedside rounds, the patient was observed to be taking frequent hot showers and reported that this relieved her persistent gastrointestinal symptoms. She admitted that she had been smoking marijuana on a regular basis since she was a teenager. For the past several years, she had experienced cyclic episodes of nausea, vomiting, and epigastric pain relieved by bathing in hot water and by avoiding cannabinoid use. For symptom relief, she reported taking a hot water shower applied to the epigastric area more than 5-6 times a day or staying in a hot water tub for an average of one hour until the water became cold. After a period of abstinence of 10 months her gastrointestinal symptoms subsided. However she resumed marijuana use, ingesting the agent baked in a brownie 2-weeks prior to admission. Urine toxicology screen was positive for THC. The features noted, including compulsive hot water bathing, chronic marijuana usage, previous resolution of symptoms with abstinence, and their return with re-exposure to the agent, were characteristic of CHS.

Nausea persisted during her hospital stay. Ondansetron was ineffective, but hot showers continued to relieve her symptoms. She did not exhibit clinical signs or symptoms of heart failure, and no significant arrhythmias were noted. She received a single dose of furosemide initially. She was then placed on labetalol 100 mg twice daily and lisinopril 10 mg daily. She was discharged to the care of her primary care physician, with instructions to avoid cannabinoid use and to continue these medications.

Discussion

Biochemical Mechanisms in Myocardial CB-1 and CB-2 Receptors

Compared to the known effects of marijuana on the gastrointestinal system, much less is known about its impact on the heart. It has been shown that CB-1 receptors are present in the heart, providing a possible pathway for cannabinoids to impact myocardial function. ^{1,9,13,16} In animal models, both endocannabinoids and THC evoke CB-1 receptor-mediated bradycardia and hypotension, and decrease cardiac contractility. ^{14,15,17} In 2003, Bonz et al used a human heart model to demonstrate that CB-1 agonism led to decreased contractility. ^{1,16,18} Models of druginduced cardiomyopathy and end-stage liver disease indicate that CB-1 antagonists, such as Rimonabant and AM-281 have a cardioprotective effect. ^{4,6,7,9,17,18,19,20}

The mechanism by which CB-1 stimulation leads to changes in myocardial function is complex. Proposed mechanisms include the involvement of both 'classical' and endothelial cannabinoid receptors resulting in the release of nitric oxide and endothelium-derived hyperpolarizing factor (EDHF), the activation of vanilloid receptors, metabolism of endocannabinoids to vasoactive molecules, and both peripheral inhibition and central excitation of the sympathetic nervous system. ^{47,19} CB-2 receptors are also expressed in the myocardium, but information on their role is very limited. Recent evidence suggests that activation of CB-2 receptors may play a role in protection against ischemia/reperfusion injury in the myocardium. ^{9,10,12,20}

Takotsubo cardiomyopathy and the Endocannabinoid Pathway

Stress cardiomyopathy, or takotsubo syndrome, has often been associated with hypercatecholaminergic states. Typical echocardiogram features include apical wall hypokinesis with contraction limited to the cardiac base, resulting in a takotsubo (or pot)-like appearance in the ventriculogram. Beta-receptor mediated sympathetic stimuli have been thought to cause regional myocardial stunning with regional differences perhaps reflecting congenital variations in concentration of the receptors. 3,5,6,13 It has been suggested that the endocannabinoid system could represent an alternative mechanism causing psychological stress that leads to cardiomyopathy. Pacher, et al, suggested that endogenously produced cannabis-like substances (endocannabinoids) have direct, as well as CB-1 mediated, cardiovascular effects. 8,10,12,15 Endocannabinoid stimulation has also been suggested as a mechanism for neurogenic myocardial stunning, seen accompanying subarachnoid hemorrhage and ischemic stroke.^{3,6,13,16} A similar mechanism could apply to exogenous cannabinoids such as marijuana, which are known to cause tachycardia with acute use, and hypotension and bradycardia with chronic use and could perhaps impair myocardial function with more intense stimulation.8,11,15,17

Despite the theoretical potential of the endocannabinoid stimulation leading to cardiomyopathy, cardiac complications were notably absent from the Simonetto series. 6,9,16,18 Kaushik postulated that activation of the endocannabinoid system (described above) might explain the association. While the presentation in terms of regional myocardial involvement differs, the patient described here, as well as the one in Kaushik, et al's, study, presented with a form of takotsubo cardiomyopathy.

Limitations

It is by no means certain that the association described here and in the one other case report, has a pathophysiologic basis, rather than being merely coincidental. Limitations to concluding that cannabinoids caused takotsubo cardiomyopathy include the following. First, emotional stress factors could have triggered takotsubo cardiomyopathy via the sympathetic pathway, and cannot be excluded in this patient. It is possible that CHS may have been a coincidental comorbidity. Second, available marijuana products can contain potentially dangerous contaminants including molds, pesticides, lead, and other substances. 11,14 Such ingredients could have contributed to myocardial stunning and

carcinogenesis. Third, marijuana use is extremely common, and it seems unlikely that a causative relationship to cardio-myopathy would have escaped notice for so long. Moreover, it is unclear why CHS itself has only been relatively recently reported in the literature, with the earliest case report published in 2004. ^{19,18} A possible reason could be an increase in THC concentration in available marijuana. Selective breeding of the *Cannabis sativa* plant has increased the average THC content documented in police seizures around the world from 0.75% to as high as 16%. ^{5,14,19} In addition, marijuana use in the United States has risen in the past decade. ^{1,10,20} This increased intensity of the exposure (THC content) and the size of the population exposed could have contributed to the increased reports of toxic effects such as CHS.

Conclusion

This case report describes an unusual case of the mid-ventricular variant of takotsubo cardiomyopathy associated with CHS in a long-term marijuana user. The clinical findings of CHS are discussed, as is the pathophysiology of the two conditions. A true pathophysiologic relationship between them is uncertain, but could possibly represent exogenous cannabinoid stimulation leading to both CHS and myocardial stunning, through mechanisms discussed above.

There is a high prevalence of cannabinoid usage in Hawai'i and instances of CHS are likely to be encountered. This case report hopes to increase awareness of CHS, and of the possibility that there may be a relationship to cardiomyopathy.

Conflict of Interest

None of the authors identify a conflict of interest.

Authors' Affiliations:

- Department of Medicine, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (MN)
- The Queens Medical Center, Cardiovascular Division, Honolulu, HI; and John A. Burns School of Medicine. University of Hawai'i. Honolulu. HI (DF)
- Division of Cardiology, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (JMCC)

Correspondence to:

Masayuki Nogi MD; 1356 Lusitana Street, 7th Fl., Honolulu, HI, 96813; E-mail: mnogi@hawaii.edu

- Hawai'i State Specific Tables with Percentages, Numbers in Thousands. 2010-2011 NSDUH. http://www.samhsa.gov/data/NSDUH/2k11State/NSDUHsae2011/NSDUHsaeHI2011.pdf. 2013:1-2. Available at: http://www.samhsa.gov/data/NSDUH/2k11State/NSDUHsae2011/ NSDUHsaeHI2011.pdf.
- Felder CC, Glass M. Cannabinoid receptors and their endogenous agonists. Annu Rev Pharmacol Toxicol. 1998;38:179–200. doi:10.1146/annurev.pharmtox.38.1.179.
- Jin KL, Mao XO, Goldsmith PC, Greenberg DA. CB1 cannabinoid receptor induction in experimental stroke. Ann Neurol. 2000;48(2):257–261.
- Taché Y. Cyclic vomiting syndrome: the corticotropin-releasing-factor hypothesis. Dig Dis Sci. 1999;44(8 Suppl):79S–86S.
- Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. Circulation. 2008;118(4):397–409. doi:10.1161/CIRCULATIONAHA.106.677625.
- Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc. 2012;87(2):114–119. doi:10.1016/jj.mayocp.2011.10.005.
- Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. Pharmacol Ther. 2010;126(1):21–38. doi:10.1016/j.pharmthera.2009.12.005.
- Niederhoffer N, Szabo B. Effect of the cannabinoid receptor agonist WIN55212-2 on sympathetic cardiovascular regulation. Br J Pharmacol. 1999;126(2):457–466. doi:10.1038/sj.bjp.0702337.
- Cardiovascular regulation. Br J Pharmacol. 1999; 12c(2):497–400. doi:10.1038/sj.bjb.0702337.
 Allen JH. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut. 2004;53(11):1566–1570. doi:10.1136/gut.2003.036350.
- Pacher P, Mukhopadhyay P, Mohanraj R, Godlewski G, Bátkai S, Kunos G. Modulation of the endocannabinoid system in cardiovascular disease: therapeutic potential and limitations. *Hypertension*. 2008;52(4):601–607. doi:10.1161/HYPERTENSIONAHA.105.063651.
- McLaren J, Swift W, Dillon P, Allsop S. Cannabis potency and contamination: a review of the literature. Addiction. 2008;103(7):1100–1109. doi:10.1111/j.1360-0443.2008.02230.x.
- Kaushik M, Alla VM, Madan R, Arouni AJ, Mohiuddin SM. Recurrent stress cardiomyopathy with variable regional involvement: insights into etiopathogenetic mechanisms. Circulation. 2011;124(22):e556–7. doi:10.1161/CIRCULATIONAHA.111.059329.
- Bouchard J-F, Lépicier P, Lamontagne D. Contribution of endocannabinoids in the endothelial protection afforded by ischemic preconditioning in the isolated rat heart. Life Sci. 2003;72(16):1859–1870.
- Nicolson SÉ, Denysenko L, Mulcare JL, Vito JP, Chabon B. Cannabinoid hyperemesis syndrome: a case series and review of previous reports. *Psychosomatics*. 2012;53(3):212–219. doi:10.1016/j.psym.2012.01.003.
- Dewey WL, Harris LS, Howes JF, et al. Pharmacology of some Marijuana Constituents and Two Heterocyclic Analogues. Nature. 1970;226(5252):1265–1267. doi:10.1038/2261265a0.
- Bonz A, Laser M, Küllmer S, et al. Cannabinoids Acting on CB1 Receptors Decrease Contractile Performance in Human Atrial Muscle. *Journal of Cardiovascular Pharmacology*. 2003;41(4):657.
- Lim SY, Davidson SM, Yellon DM, Smith CCT. The cannabinoid CB1 receptor antagonist, rimonabant, protects against acute myocardial infarction. Basic Res Cardiol. 2009;104(6):781– 792. doi:10.1007/s00395-009-0034-2.
- Mukhopadhyay P, Bátkai S, Rajesh M, et al. Pharmacological inhibition of CB1 cannabinoid receptor protects against doxorubicin-induced cardiotoxicity. *Journal of the American College* of Cardiology. 2007;50(6):528–536. doi:10.1016/j.jacc.2007.03.057.
- Randall MD, Kendall DA, O'Sullivan S. The complexities of the cardiovascular actions of cannabinoids. Br J Pharmacol. 2004;142(1):20–26.
- Defer N, Wan J, Souktani R, et al. The cannabinoid receptor type 2 promotes cardiac myocyte and fibroblast survival and protects against ischemia/reperfusion-induced cardiomyopathy. FASEB journal. 2009;23:2120–2130. doi:10.1096/fj.09-129478.

MEDICAL SCHOOL HOTLINE

The Pacific Basin Rehabilitation Research and Training Center at the John A. Burns School of Medicine: Thirty Years of Service to Hawai'i and Beyond

Violet E. Horvath PhD, MSW, MFA

The Medical School Hotline is a monthly column from the John A. Burns School of Medicine and is edited by Satoru Izutsu PhD; HJMPH Contributing Editor. Dr. Izutsu is the vice-dean of the University of Hawai'i John A. Burns School of Medicine and has been the Medical School Hotline editor since 1993.

Introduction

In 1983 a Request for Proposals (RFP) from the National Institute on Disability and Rehabilitation Research (NIDRR) in Washington DC, caught the attention of Dean Terence A. Rogers (1972-1988) at the John A Burns School of Medicine (JABSOM) at the University of Hawai'i. NIDRR is housed under the Office of Special Education and Rehabilitative Services of the US Department of Education. The project was to be co-directed by Dr. Gary Okamoto, a physiatrist at the Rehabilitation Hospital of the Pacific in Honolulu, Hawai'i, and Dr. Satoru Izutsu, a licensed psychologist and a registered occupational therapist at JABSOM.

The application process was successful, and the Pacific Basin Rehabilitation Research and Training Center (PBRRTC) was established in 1984. The focus was primarily on Micronesia, although other territories and islands were included. The RFP was a 10-year Federal grant to work with persons with all types of disabilities post-discharge from the Rehabilitation Hospital of the Pacific. The goal was to provide a bridge for physical and vocational rehabilitation. In addition, JABSOM sought to promote a residency program in physiatry at the Rehabilitation Hospital of the Pacific.

In time PBRRTC relocated to an office on Young Street in Honolulu, and the grant ended. It looked as though PBRRTC might close its doors. The Director at the time, Dr. Dan Anderson, began submitting small proposals for grants in Hawai'i, and the PBRRTC began to take on the form it has today.

Thirty years after its establishment, PBRRTC continues to advocate for persons of all ages who have all types of disabilities. While PBRRTC's mission remains the same, many changes have taken place. In 2013 the Center moved to the Gold Bond Building, near the John A. Burns School of Medicine. A new website was launched in January 2014 (jabsom.hawaii.edu/pbrrtc). A monthly electronic newsletter, which began in October 2013, provides information on topics related to PBRRTC's projects to a broad audience. Past editions of the newsletter (which may be accessed from the website, where one can also sign up to receive the newsletter) included information on World Stroke Day, National Heart Month, National Mentoring Month, and

Brain Injury Awareness Month; building designs that work for persons who are deaf or hard-of-hearing; depression as the second most common cause of disability worldwide; veterans and traumatic brain injuries; products designed for those with sight loss so they may live independently; and how strokes are affecting young people.

Currently PBRRTC is a part of the Research Corporation of the University of Hawai'i (RCUH). It continues to assist agencies and organizations that lack the expertise and/or personnel to accomplish their goals and tasks. Increasingly, PBRRTC's projects involve the use of technology. Most of PBRRTC's current projects are one-year contracts with the possibility of renewal. Sustainability remains a challenge for PBRRTC.

Current Projects

PBRRTC is funded solely through support it receives from grants and contracts. Staff members currently work on eight projects. One project is funded by the Hawai'i Department of Health, Developmental Disabilities Division, while the remaining seven are with the Hawai'i Department of Health's Division of Vocational Rehabilitation (DVR). The diversity of the projects described below demonstrates the breadth of assistance PBRRTC offers.

Hawai'i Neurotrauma Registry Project. Entering its second year is the Hawai'i Neurotrauma Registry Project. The project is funded through the Neurotrauma Special Fund, which is derived from surcharges resulting from traffic citations that contribute to neurotrauma injuries. While the State is limited on how the funds can be used, a registry is allowed. The Neurotrauma Special Fund is administered by the Department of Health, Developmental Disabilities Division, Outcomes and Compliance Branch. Their mission includes a focus on neurotrauma supports.

The goal of this longitudinal project is to better understand the ongoing needs of neurotrauma survivors and their families. The information in turn will help justify the need for funding and coverage of direct services. For purposes of the registry, "neurotrauma" refers to traumatic brain injury and concussion, stroke, and/or spinal cord injury. It includes any Hawai'i state resident of any age who at any time in their life experienced one or more of these injuries. This voluntary registry is unique in that it focuses on and interviews survivors of these traumas, rather than relying on static records such as death certificates, Medicaid data, or discharge, emergency medical services, or transportation department records, which are used by most national and state registries.

The Hawai'i Neurotrauma Registry Project also provides information and referrals to persons with neurotrauma injuries and their families. Education is a major component of the project. Staff members distribute materials on preventing neurotrauma injuries and related information statewide at events such as the Senior Fair/The Good Life Expo, neighborhood board meetings, ESPN Sports Festival, Boys & Girls Clubs, Children & Youth Day, New Baby Expo, wellness fairs, Project Grad fundraisers, support groups, the Special Parent Information Network conference, Mothers Against Drunk Driving events, and many more. They also talk about the registry to hospitals, agencies and organizations, physicians, and other groups who work with or serve persons with neurotrauma injuries. Plans include starting a quarterly electronic newsletter in April 2014 focusing on resources and news about the project.

Persons with these neurotrauma injuries are invited to participate in the registry. The survey is available online at http://svy.mk/1a5Ya5m. Assistance with the survey and more information can be sought at 808-692-1375 or HawaiiNT@hawaii.edu.

The remaining seven projects are funded through contracts with the Division of Vocational Rehabilitation. PBRRTC has a lengthy history of working with DVR. Current projects include the Comprehensive Service Center, Automated Case Management System, Consumer Satisfaction Survey, Data Analysis and Reports, Electronic Communications, Social Security Income Reimbursement, and Technical Assistance.

- (1) Comprehensive Service Center (CSC). PBRRTC is working on a 5-year strategic and business plan for a Comprehensive Service Center (CSC). The CSC is envisioned to be a one-stop center for persons who are deaf, deaf-blind, or hard-of-hearing. Services provided could include assistance with reading mail; help with filing taxes; leisure and personal growth classes; and classes that help provide pathways to higher education and employment. Challenges include sustainability of the CSC and service provision to persons on all islands. Staff members and a facilitator will hold stakeholder and public meetings to obtain input on the center and feedback on the strategic and business plan.
- (2) Automated Case Management System (ACMS). PBRRTC provides professional guidance and expertise as DVR moves from a decades-old computer system to a new electronic case management system that is more flexible and will yield more information. The shift was directed by the Fiscal Year 2007 Monitoring Report on the Vocational Rehabilitation and Independent Living Programs in the State of Hawai'i¹. PBRRTC

staff members provide technical oversight, technical support, facilitate solutions when challenges arise, develop and update contingency plans, and produce and assist in producing necessary project documentation, among other tasks. The automated case management system is on schedule for a launch in fall 2014.

- (3) Consumer Satisfaction Survey (CSS). The Rehabilitation Act (Sec. 105(c)(4))² prioritizes a review and analysis of the effectiveness of and consumer satisfaction with Vocational Rehabilitation (VR) services and services provided by other State, public, and private entities that work with persons with disabilities. For many years, DVR has contracted with PBRRTC to develop and administer the survey. On a quarterly basis, a confidential survey is mailed to individuals whose cases recently closed with or without employment. The voluntary survey may also be filled out online and includes questions about access to VR services, working with VR counselors, services received from agencies other than VR, current employment (if any), access to information, and overall view of VR. Participants end the survey by answering open-ended questions about what they like about VR, what they would like to see changed or added, and any other comments they wish to share.
- (4) Data Analysis and Reports. Section 106 of the Rehabilitation Act of 1973,^{3,4} as amended, requires the Rehabilitation Services Administration to establish evaluation standards and performance indicators for vocational rehabilitation programs that include outcome and related measures of program performance. PBRRTC assesses Vocational Rehabilitation Services Outcomes by analyzing and reporting information that includes potential strategies for the improvement of services. Quarterly reports, an annual report, and a report on transition-aged youth (16-24) are the main products under this project.
- (5) Electronic Communications. Beginning in July 2014, PBRRTC will assist DVR in developing, reviewing, and updating websites and social media to better serve their clients. The goal is to design accessible electronic communications that will reach a wide range of consumers and the public for purposes of outreach, data collection, social support, and other needs.
- (6) Social Security Income Reimbursement. Another project that begins July 2014 provides training and technical assistance in order to develop a system for monitoring participation in the Social Security Administration's Ticket to Work Program⁵. The Ticket to Work Program is free and voluntary for persons ages 18-64 who have a disability and receive Social Security Disability Insurance (SSDI) or Supplemental Security Income (SSI) benefits. The purpose is to increase the financial independence and self-sufficiency of beneficiaries by offering expanded choices in services and supports when they are entering, reentering, and/or maintaining employment. The services could include training, career counseling, vocational rehabilitation, job placement and ongoing support services. PBRRTC will act as a liaison between DVR and the Ticket to Work Program; plan,

develop, and maintain a system to track "Tickets"; monitor program changes and issues; and evaluate the effectiveness of the program on an annual basis, among other duties.

(7) Technical Assistance. At the request of DVR, PBRRTC provides technical assistance on topics related to vocational rehabilitation. These may include the provision of advice, assistance, or training, such as data production and management, and support of project design, development, and implementation. It may involve the systematic gathering of data to determine the current status of a particular issue, developing strategies for improvement, and includes assistance to cooperating agencies and organizations.

Since its inception in 1984, PBRRTC has assisted countless persons with all types of disabilities. It has conducted research, evaluated projects, mentored and provided support to individuals with disabilities, and educated the public, among the many services it has provided. PBRRTC plans to continue being a voice for those who might not otherwise be heard for the foreseeable future.

Author's Affiliation:

- Interim Director, Pacific Basin Rehabilitation Research and Training Center, the Research Corporation of the University of Hawai'i.

- U.S. Department of Education, Office of Special Education and Rehabilitative Services, Rehabilitation Services Administration. Fiscal Year 2007 Monitoring Report on the Vocational Rehabilitation and Independent Living Programs in the State of Hawaii. http://www2.ed.gov/rschstat/eval/rehab/107-reports/2007/hi.pdf. Accessed March 3, 2014.
- Pennsylvania Rehabilitation Council. Excerpt 1998 Amendment to Rehabilitation Act of 1973. http://www.parac.org/rehabact.html. Accessed March 3, 2014.
- U.S. Department of Education. Evaluation Standards and Performance Indicators for the Vocational Rehabilitation Services Program. http://www2.ed.gov/rschstat/eval/rehab/standards. html. Updated January 16, 2014. Accessed March 3, 2014.
- The Library of Congress. Committee Reports, 113th Congress (2013-2014), House Report 113-014 – Part 1, Supporting Knowledge and Investing in Lifelong Skills Act. http://thomas.loc.gov/cgi-bin/cpquery/?&sid=cp113hjA05&r_n=hr014p1.113&dbname=cp113&&sel=TOC_552441&. Accessed March 3, 2014.
- Social Security Administration. Ticket Overview. http://www.ssa.gov/work/overview.html#a0=0. Accessed March 11. 2014.

INSIGHTS IN PUBLIC HEALTH

Perspectives on Pain in the Low Back and Neck: Global Burden, Epidemiology, and Management

Maria Vassilaki MD, PhD, MPH and Eric L. Hurwitz DC, PhD

Insights in Public Health is a monthly solicited column from the public health community and is coordinated by HJMPH Associate Editors Jay Maddock PhD from the Office of Public Health Studies at John A Burns School of Medicine and Donald Hayes MD, MPH from the Hawai'i Department of Health in collaboration with HJMPH Manuscript Editors Tonya Lowery St. John MPH and Ranjani Starr MPH from the Hawai'i Department of Health.

Introduction

Low back pain (LBP) is a major public health problem worldwide. All age groups are affected, including children and adolescents,1 with 1%-2% of adults in the United States being disabled as a result.² Back and neck pain (NP) are two of the most common reasons for visits to primary care physicians and chiropractors in the United States and cause considerable disability and financial burden.3 Although people don't die from low back or neck pain, the morbidity toll is enormous from both personal and societal perspectives. Both are reported by more patients and have a higher impact in the workforce, as well as financially, than any other musculoskeletal disorder and most other clinical conditions. 4 In 2005 only heart disease and stroke had substantially higher medical expenditures than spine disorders in the United States.⁵ The large and rising spine-related health-care expenditures over the last decade do not seem to be associated with improved self-assessed health status, or improvement in functional ability, work limitations or social functioning.⁵ In this article, we take a step back to look at this toll, and look ahead to see where we, as individuals and as a society, should go in order to reduce the burden of back and neck pain.

Global Burden of Disease — Low Back and Neck Pain

In studies that measure the Burden of Disease (BoD), diseases are ranked according to how much death and disability they cause.⁶ The BoD estimates are useful to governments and organizations when planning for health priorities, usage of resources, and assessing costs or benefits of interventions in the public health sector.⁶ Disability adjusted life years (DALYs) is an overall summary measure of population health that the global BoD uses, which combines years of life lost due to premature mortality (YLLs) and years lived with disability (YLDs).⁷ LBP is presently the leading cause of disability in the world.⁷ Case definitions of LBP are quite variable, thus estimation of the global burden is not as easy as it would seem.⁷ According to the Global Burden of Disease (GBD) 2010, LBP results in more disability than any other condition worldwide (10.7% of total YLDs; ranks 6th in terms of overall disease burden [83]

million DALYs]); and is the leading cause of disability in both developed and developing countries.⁸ These estimates are up significantly from the GBD 2000-2004 estimates (eg, LBP was ranked 105 out of 136 conditions in terms of YLDs); however, as LBP was defined differently, the GBD estimates cannot be used to assess trends over time.⁷ Given the above estimates, however, LBP is a condition that demands our attention in research, public health, and patient health-care.

NP is also one of the major causes of disability globally. The 2010 GBD estimates reflect the fact that both NP prevalence and burden is high around the world. As case definitions of NP are also quite variable, the NP global burden is not easy to estimate either; however, it is based on an extensive series of systematic reviews capturing a large number of studies. Among 291 other health conditions, NP ranked 4th in terms of disability (in YLDs) and 21st in overall burden of disease (in DALYs).

Epidemiology of Low Back Pain

Major indicators of disease occurrence used in epidemiologic studies are incidence (number of new cases in a given period of time) and prevalence (number of individuals having the disease at a given point or period in time).9 Although LBP is often seen as a condition with individual events characterized by episode duration (eg, acute: less than 6 weeks; sub-acute: 6-12 weeks; chronic: more than 12 weeks)¹⁰ epidemiologic studies are not suggestive of a model of back pain as a series of separate unrelated events but rather as a long-term condition.¹¹ Currently there are discussions of models that follow the lifecourse epidemiology approach, exploring long-term processes (ie, biological, behavioural, psychosocial, etc.) that associate adult health conditions with exposures in gestation, childhood and adolescence, earlier adulthood and even across generations. 11 It is quite clear that back pain for example is common among children and especially in adolescents, suggesting that episodes of pain in adulthood might have resulted from earlier in life exposures.11

Prevalence and Incidence

Most people will experience LBP at some point in their lifetime, with two-thirds having a recurrence and one third having periods

of disability.⁴ One-year recurrence estimates range from 24% to 80%.¹² As longitudinal studies are much more expensive than cross-sectional ones, there are multiple studies reporting on LBP prevalence but fewer reporting on incidence. The 1-year first-ever LBP incidence has been estimated between 6.3% and 15.4%, while the 1-year (overall) incidence ranges from 1.5% to 36% (ie, first-ever or recurrent LBP incidence).¹² However, we need to note that these studies only take into account the first episode in the year and do not consider repeat episodes, resulting likely in underestimation of LBP episode incidence in that time period.

When prevalence is estimated, we are limited in making between-population comparisons, as there is methodological variability across studies due to different case definitions, the recall period, the validation of the instruments used, or the representativeness of the sample, among other issues. Estimates of LBP point prevalence in general population samples range from 1.0% to 58.1% (mean: 18.1%; median: 15%) and 1-year prevalence from 0.8% to 82.5% (mean 38.1%; median 37.4%).¹² Studies that specify a minimum episode duration (eg, 1 day) have lower prevalence estimates than ones without definitions of episode duration. Heterogeneity in case definitions are known to have large effects on LBP prevalence estimates. ¹² For example, descriptions such as "back pain," "low back pain," and "pain on the posterior aspect of the body from lower margin of 12th rib to lower gluteal folds" result in different prevalence estimates. In other systematic reviews, point prevalence ranges from 12% to 33% and 1-year prevalence from 22% to 65%. 13 Prevalence estimates are higher in surveys of self-reported LBP than when medical care data are used (eg, 28%-40% in surveys vs 12%-15% with medical data). Such variable prevalence estimates and the uncertainty with which they have been estimated preclude accurate estimates of prevalence change over time.²

Recurrence, Duration, and Remission

LBP can be described as a long-term, recurrent condition that follows many different trajectories rather than as an acute, sub-acute or chronic condition. ^{11,14} Cases in which LBP never recurs are rare; many patients, suffering between episodes, change what they do to manage recurrences. LBP episode duration estimates range from a median of 42 days from the start of the episode ¹⁵ to 128.5 pain days for LBP lasting between 3 to 6 months. ¹⁶ Remission at 1-year has been estimated at 54% and 90%. ¹²

Risk and Prognostic Factors

There are several factors that influence the onset and course of LBP. Some of these factors are modifiable, while others are not. A previous episode of back pain is the primary risk factor for a new LBP episode. As reviewed by investigators, age is a risk factor, with prevalence increasing up to 60 or 65 years of age, with reports pointing out that prevalence keeps increasing with increasing age for more severe and disabling back pain. The third decade of life has been noted as having the highest LBP incidence. Although findings are not consistent, some studies have found that LBP prevalence might be higher among older

women compared to older men, while others have estimated that women are more likely to take time off work, use LBP-related health care, or develop chronic LBP.¹² Low educational and social status have been associated with higher prevalence and incidence of LBP, as reviewed by authors.¹²

Obesity has been associated with an increased risk of LBP, which might be stronger in women.¹⁷ Psychosocial factors, such as stress, anxiety or depression, have been associated with not only the occurrence but also the transition to chronic LBP, although the direction of the association often is not clear. Workplace psychosocial factors (eg, job dissatisfaction, stress, monotonous tasks, or lack of social support and poor work relations) have been associated with occurrence or transition to chronicity. Although data are limited, physical work demands such as twisting, bending, whole-body vibration or manual handling, are likely LBP risk factors.¹⁸

Personal and Societal Impacts

LBP is the leading cause of activity limitation and workplace absence in most parts of the world. The consequences of LBP are vast and affect the individual, family, health-care systems, industry, and the economy. This can be attributed to restrictions in physical capabilities, participation, work related and financial burden, use of health-care resources, etc. Such impacts differ depending on access to health care, socio-economic status, and occupation distributions in the community. Direct back pain health-care expenditures in the United States were \$90.7 billion in 1998. The burden is even greater when indirect costs such as productivity losses, indemnity pay, litigation, retraining and other administrative costs are considered. 12

Epidemiology of Neck Pain

NP is a common condition in many regions of the world and is increasing in the general population, as well as, in specific occupations. As with LBP, most people will have NP at some point in time, and also like LBP, case definitions are highly variable. One study notes 300 different definitions used in epidemiologic studies, mainly pertaining to the anatomical region and the recall period. 20

Prevalence and Incidence

NP is typically first experienced during childhood or adolescence, running an episodic course over time. As with LBP, cross-sectional studies are much more common than longitudinal studies. In a systematic review, the 1-year NP incidence ranged from 10.4% to 21.3%. Studies have shown that NP incidence varies by occupation, with office and computer workers, healthcare workers, and transit operators having a high incidence of neck disorders.

Due to considerable methodological heterogeneity in epidemiologic studies it is difficult to compare prevalence estimates between studies in different populations. Researchers have also pointed out that "activity-limiting" NP has a lower prevalence than "any" NP. In a recent systematic review, the NP point prevalence in the general population ranged between 0.4% and

41.5% (mean: 14.4%) while 1-year prevalence ranged between 4.8% and 79.5% (mean: 25.8%), with differences largely resulting from heterogeneity of methods and case definitions.⁹

Remission, Duration, and Recurrence

Many epidemiologic studies define as NP remission, the transition to an asymptomatic state, regardless of future NP episodes. However, it is quite challenging to estimate with accuracy the time to remission. In a systematic review, remission at 1 year was estimated between 33% and 65% and 50%-85% of persons with neck pain in general population samples have reported neck pain 1 to 5 years later. However, a better description of the course of neck pain is needed.

Risk and Prognostic Factors

There are several personal and environmental factors associated with increased risk of NP or its course. Age and NP onset are associated, and several studies have estimated a lower NP incidence in men.⁹ Poor self-assessed health, as well as psychological status, previous episodes of NP or LBP, occupation, workplace factors (eg, job dissatisfaction, sedentary work positions, and poor physical work environments), ethnicity, or smoking may be associated with NP onset.⁹ Several factors might also be prognostic. It is not clear whether gender is one of those factors, with a possibility for men to be more likely to have a remission over a 1 or 5 year-period. Younger persons are generally more likely to remit, and a previous neck injury, poor self-rated health, poor psychological health, getting angry or frustrated, worrying, or high pain intensity may also be associated with poor NP outcomes.²²

Personal and Societal Impacts

As noted for LBP, the consequences of NP and related disability are substantial and affect individuals, families, health-care systems, industry, and economies. Patients might have limitations in daily activities such as driving, turning their head, working on the computer, and participating in work, family, community, and sporting activities. Consequences of NP vary depending on several factors related to onset and prognosis, including socioeconomic status, access to health care, and occupations in the community, with low-income countries generally affected more than others. Economic impact is also substantial, especially when both direct and indirect costs are considered, ie, health-care costs, work absenteeism, insurance.

Management

The numerous patients with spine disorders together with our generally poor understanding of etiology has resulted in an overwhelming variety of potential treatments.² It is recommended that each patient with LBP or NP go through a screening protocol during their health-care provider visit to rule out less common cases of serious spinal pathology and neurologic conditions, assess patients at higher risk for spinal disorders, and guide any further testing or imaging. The vast majority of cases do not present with serious underlying pathology or other

red flags. Multiple therapeutic interventions are available with mostly small effects in the short-term and uncertain effects in the long run. Many interventions are not evidence-based and have serious potential side effects and high complication rates (including death).² Spine-related health-care use rates are on the rise for reasons not entirely clear, but probably because of a combination of factors including increasing prevalence of more chronic pain, changing beliefs about pain and pain management, increased use of high-cost interventions, inappropriate and overuse of diagnostic imaging, and rising costs of pharmaceuticals and surgical devices, among other factors.² A very important component of patient care is the assessment of treatment outcomes. For instance, there are six main domains relevant to the assessment of LBP: pain symptoms, function, well-being, work, disability, and satisfaction with care,23 and instruments have been developed to assess these domains. Very important also is the concept of "minimal clinically important change" (MCIC), which represents the smallest individual change score important for the patient. For many instruments measuring pain and disability, a 30% change in a patient's score has been suggested as a satisfactory MCIC for improvement.²⁴ In addition, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group suggests the use of an outcome measure that is a composite of at least two patient outcome measures including pain, function, emotional well-being, and global assessment of improvement.²

Management of Low Back Pain

Non-surgical Care: Treatments, Outcomes, and Controversies

There are several non-surgical interventions used for LBP. For acute LBP, for example, interventions include brief education, reassurance, advice to stay active, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), spinal manipulation and other manual therapies, and physical modalities such as heat and ultrasound, among many others.1 For chronic LBP, recommendations include education, advice to stay active, NSAIDs, exercise, manual therapies, and self-management activities, etc. However, non-surgical interventions have not been without controversies. For example, although being physically active is supported by strong evidence for reducing disability, data are conflicting for the clinical and cost effectiveness of physical therapy in chronic back pain. The use of opioids for chronic LBP is also controversial because of concerns about the potential for abuse, questionable effectiveness, and high mental illness co-morbidity with chronic LBP.² People using opioids for back pain are more likely to have underlying anxiety, depression and other psychiatric conditions that impair prognosis.²

Surgical Care: Treatments, Outcomes, and Controversies

Interventional spine procedures range from percutaneous injections (eg, epidural steroid injections [ESIs], facet/zygapophysial joint procedures, intradiscal procedures, etc.) to surgery (eg, discectomy, spinal canal decompression, spinal fusion, etc.).² Both the techniques used and the usage rates of several

procedures have increased dramatically over the past decade, however supporting evidence for many of these interventions is limited. If for example we take a look at ESIs, their increase in use might be more associated with economic than clinical factors (though short-term pain relief in specific cases can offer substantial clinical benefits).²

The frequency of back surgery in the United States is the highest in the world²⁵ and the rate continues to increase.²⁶ Spinal fusions increased by 40% between 1998 and 2004 and the rate of complex fusion procedures for lumbar spinal stenosis increased 15-fold between 2002 and 2007. Such increases in spinal fusion cannot easily be explained, but may be related to availability of technologies with inadequate data on their superiority over established techniques with known risk-benefit profiles.² When LBP is not accompanied by serious neurologic deficits or for nonradicular persistent LBP, the risks of surgery may outweigh the benefits. However, for radiculopathy with herniated lumbar disc or for spinal stenosis with symptomatology, surgery is indicated in the presence of serious or progressive neurologic deficits.²⁷ In a recent systematic review on surgery for LBP,²⁷ fusion was not more effective than intensive rehabilitation for nonradicular back pain, although compared to standard nonsurgical care it was associated with small to moderate benefits. On the other hand, for radiculopathy with herniated lumbar disc and spinal stenosis with symptomatology, surgery was associated with short-term benefits when compared to nonsurgical therapy, although in the long-run such benefits generally declined over

Two systematic reviews²⁸⁻³⁰ commissioned by the Yale University Open Data Access (YODA) Project used patient level meta-analyses of RCT data obtained by the manufacturer to study the effectiveness and harms of recombinant human bone morphogenetic protein-2 (rhBMP-2) compared to autologous iliac crest bone grafting in spine fusion. Both reviews concluded that there was no clinically important difference in inducing spinal fusion by either the rhBMP-2 or autologous iliac crest bone grafting, and both had similar complications when used in anterior lumbar interbody fusion or posterolateral fusion as summarized by Resnick, et al.31 Compared to autograft in anterior cervical surgery, however, rhBMP-2 had more complications and ectopic bone formation in posterior lumbar interbody fusion.31 These findings of rhBMP-2 harms and questionable benefits are consistent with the prior review that precipitated the YODA project, ³² underscoring the need for systematic and complete reporting of benefits and harms, skepticism about the clinical benefits of new technology until evidence emerges from scientifically sound studies, and for patients to be fully engaged in decisions about their care.

Management of Neck Pain

Non-surgical Care: Treatments, Outcomes, and Controversies

There are multiple non-surgical treatments for NP and whiplash-associated disorders (WAD). Non-surgical therapeutic interventions include among others education and advice, exercises,

manual therapies (eg, mobilization, manipulation, massage), physical modalities (eg, transcutaneous electrical nerve stimulation [TENS], ultrasound, diathermy, low-level laser therapy), collars, acupuncture, medication (eg, analgesics, steroids, NSAIDs), or combinations of treatments (eg, mobilization and exercises). In a best evidence synthesis (1980-2006), it was found that educational video exercises and mobilization were more effective than usual care or physical modalities for WAD.³³ For other NP, supervised exercises and manual interventions, low-level laser therapy and perhaps acupuncture were more effective than other treatments, or no treatment, although none of the treatments were judged as superior in the short or long run.33 In particular, evidence of long-term effects was lacking for all non-invasive (non-surgical) interventions and the optimal amount of non-surgical treatment needed was also unclear, as no dose-response (ie, higher frequency of treatments results in better outcomes) or dose-duration (ie, longer duration of care results in better outcomes) relationships were detected. In addition, insufficient data on effective non-surgical interventions for acute non-traumatic neck disorders and Grade III neck pain (disorders with radiation and neurologic signs) precluded any meaningful clinical inferences.³³

Surgical Care: Treatments, Outcomes, and Controversies

Surgical care is often recommended for patients with NP; however, surgery is costly and exposes patients to inherent serious risks and perioperative pain, morbidity, and complications. When care focuses on conditions of specific pathologic etiology, surgical treatments could be the only solution (eg, after some acute injuries, neoplasms or spinal infections). Most NP cases, however, are not accompanied by aggressive pathology and are not in need of immediate surgical intervention. Nevertheless, surgical care is often performed for NP without serious underlying pathology and its effectiveness is not currently well understood.³⁴

In a best evidence synthesis of the limited available literature on surgical interventions for neck pain without serious underlying pathologic conditions, support was lacking for open or percutaneous surgeries in patients with only NP without radicular symptoms or evident serious pathology, while surgical treatment and injections for cervical radicular symptomatology might be appropriate for patients with severe impairments.³⁴

Discussion

Enhancing Prevention, Improving Prognosis, and Reducing harms

Based on current knowledge it is not possible, in most cases, to prevent a first-ever (primary) episode of back or neck pain.⁴ Recurrences, however, together with the disability and remaining "costs" to the individual and society could be the target of prevention efforts. Health promoting recommendations for multiple chronic diseases, such as physical activity, smoking cessation or maintaining a healthy weight, might also have protective effects on back pain.⁴ Having said that, we know that we have a lot of work to do, as for example currently none of

the interventions are backed up with strong evidence for their effectiveness in preventing recurrences of back pain, with the possible exception of physical exercise in reducing the number and duration of recurrences.⁴

It is challenging to study and treat spine disorders due to variability in clinical presentation, in case definitions used, in course or prognosis, as well as in treatments and limited success in their effectiveness. ¹⁰ However, new models of care, borrowed from other research areas, are being introduced in spine research. For example, stratified care aims at optimizing effects, minimizing harm and increasing healthcare efficiency. ¹⁰ In such a model, it is suggested to use: (a) prognostic stratification to guide treatment (eg, reassure or offer minimal treatment to patients with low risk for poor outcomes, but more extensive treatment to those with a high risk for poor outcomes); (b) patient characteristics to guide treatment; and (c) targeted treatment to the patients most likely to respond (eg, surgery on evidence-based indications), or less likely to be harmed (eg, opioid avoidance for those at risk of dependency). ¹⁰

Conclusion

There is no reason to expect that efforts will fail in enhancing prevention, improving prognosis, and reducing harms related to LBP and NP. In fact, efforts to reduce the burden of LBP and NP might have the same or similar solutions: (a) harmonize LBP and NP case definitions and recommendations between national and international agencies, associations, organizations, and researchers; (b) conduct randomized trials to determine the effectiveness of popular interventions that lack evidence of effectiveness; (c) research all domains and domain-specific outcomes in the short- and long-term;²³ (d) explore new models of care and conceptual models that go beyond the characterization of acute or chronic episodes of pain, ie, consider pain trajectories and a life-course approach;⁴ (e) increase our knowledge of spine disorders in both developed and developing countries; (f) assure that evolving LBP and NP in the developing world receive the appropriate recognition and funding to implement culturally acceptable approaches;⁴ and (g) identify safe, effective, and cost effective interventions, as rising spine-related health expenditures have not been accompanied by population health improvement in LBP or NP.

Authors' Affiliations:

- Department of Neurology, Mayo School of Graduate Medical Education, and Division of Epidemiology, Mayo Clinic, Rochester, Minnesota (MV)
- Office of Public Health Studies, Department of Public Health Sciences, University of Hawai'i at Manoa, Honolulu, HI (ELH)

- Balague F, Mannion AF, Pellise F, Cedraschi C. Non-specific low back pain. Lancet. 2012 Feb 4;379(9814):482-91.
- Friedly J, Standaert C, Chan L. Epidemiology of spine care: the back pain dilemma. Phys Med Rehabil Clin N Am. 2010 Nov;21(4):659-77.
- Hogg-Johnson S, van der Velde G, Carroll LJ, et al. The burden and determinants of neck pain in the general population: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 2008 Feb 15;33(4 Suppl):S39-51.

- Haldeman S, Kopansky-Giles D, Hurwitz EL, et al. Advancements in the management of spine disorders. Best Pract Res Clin Rheumatol. 2012 Apr;26(2):263-80.
- Martin BI, Deyo RA, Mirza SK, et al. Expenditures and health status among adults with back and neck problems. JAMA. 2008 Feb 13;299(6):656-64.
- Hoy D, March L, Brooks P, et al. Measuring the global burden of low back pain. Best Pract Res Clin Rheumatol. 2010 Apr;24(2):155-65.
- Buchbinder R, Blyth FM, March LM, Brooks P, Woolf AD, Hoy DG. Placing the global burden of low back pain in context. Best Pract Res Clin Rheumatol. 2013 Oct;27(5):575-89.
- Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2197-223.
- Hoy DG, Protani M, De R, Buchbinder R. The epidemiology of neck pain. Best Pract Res Clin Rheumatol. 2010 Dec;24(6):783-92.
- van der Windt DA, Dunn KM. Low back pain research--future directions. Best Pract Res Clin Rheumatol. 2013 Oct;27(5):699-708.
- Dunn KM, Hestbaek L, Cassidy JD. Low back pain across the life course. Best Pract Res Clin Rheumatol. 2013 Oct;27(5):591-600.
- Hoy D, Brooks P, Blyth F, Buchbinder R. The Epidemiology of low back pain. Best Pract Res Clin Rheumatol. 2010 Dec;24(6):769-81.
- Walker BF. The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. J Spinal Disord. 2000 Jun;13(3):205-17.
- Dunn KM, Jordan K, Croft PR. Characterizing the course of low back pain: a latent class
- analysis. Am J Epidemiol. 2006 Apr 15;163(8):754-61.
 van den Hoogen HJ, Koes BW, van Eijk JT, Bouter LM, Deville W. On the course of low back pain in general practice: a one year follow up study. Ann Rheum Dis. 1998 Jan:57(1):13-9.
- Von Korff M, Deyo RA, Cherkin D, Barlow W. Back pain in primary care. Outcomes at 1 year. Spine (Phila Pa 1976). 1993 Jun 1;18(7):855-62.
- Croft PR, Papageorgiou AC, Thomas E, Macfarlane GJ, Silman AJ. Short-term physical risk factors for new episodes of low back pain. Prospective evidence from the South Manchester Back Pain Study. Spine (Phila Pa 1976). 1999 Aug 1;24(15):1556-61.
- Hoogendoorn WE vPM, Bongers PM, Koes BW, Bouter LM. Systematic review of psychosocial factors at work and private life as risk factors for back pain. Spine (Phila Pa 1976). 2000:25(16):2114–25
- Luo X PR, Sun SX, Liu GG, Hey L. Estimates and patterns of direct health care expenditures among individuals with back pain in the United States. Spine (Phila Pa 1976). 2004;29(1):79-86.
- Guzman J, Hurwitz EL, Carroll LJ, et al. A new conceptual model of neck pain: linking onset, course, and care: the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 2008 Feb 15;33(4 Suppl):S14-23.
- Cote P, van der Velde G, Cassidy JD, et al. The burden and determinants of neck pain in workers: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 2008 Feb 15;33(4 Suppl):S60-74.
- Carroll LJ, Hogg-Johnson S, van der Velde G, et al. Course and prognostic factors for neck pain in the general population: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 2008 Feb 15;33(4 Suppl):S75-82.
- Deyo RA, Battie M, Beurskens AJ, et al. Outcome measures for low back pain research. A proposal for standardized use. Spine (Phila Pa 1976). 1998 Sep 15;23(18):2003-13.
- Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine (Phila Pa 1976). 2008 Jan 1;33(1):90-4.
- Cherkin DC, Deyo RA, Loeser JD, Bush T, Waddell G. An international comparison of back surgery rates. Spine (Phila Pa 1976). 1994 Jun 1;19(11):1201-6.
- Deyo RA, Gray DT, Kreuter W, Mirza S, Martin BI. United States trends in lumbar fusion surgery for degenerative conditions. Spine (Phila Pa 1976). 2005 Jun 15;30(12):1441-5; discussion 6-7.
- Chou R, Baisden J, Carragee EJ, Resnick DK, Shaffer WO, Loeser JD. Surgery for low back pain: a review of the evidence for an American Pain Society Clinical Practice Guideline. Spine (Phila Pa 1976). 2009 May 1;34(10):1094-109.
- Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. *Ann Intern Med*. 2013 Jun 18:158(12):890-902.
- Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. Ann Intern Med. 2013 Jun 18:158(12):877-89.
- Laine C, Guallar E, Mulrow C, et al. Closing in on the Truth About Recombinant Human Bone Morphogenetic Protein-2: Evidence Synthesis, Data Sharing, Peer Review, and Reproducible Research. Ann Intern Med. 2013 Jun 18;158(12):916-8.
- Resnick D, Bozic KJ. Meta-analysis of Trials of Recombinant Human Bone Morphogenetic Protein-2: What Should Spine Surgeons and Their Patients Do With This Information? Ann Intern Med. 2013 Jun 18;158(12):912-3.
- Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. The Spine Journal. 2011: 11:471-91.
- Hurwitz EL, Carragee EJ, van der Velde G, et al. Treatment of neck pain: noninvasive interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 2008 Feb 15;33(4 Suppl):S123-52.
- Carragee EJ, Hurwitz EL, Cheng I, et al. Treatment of neck pain: injections and surgical interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 2008 Feb 15;33(4 Suppl):S153-69.

I'D RATHER A BOTTLE IN FRONT OF ME THAN A FRONTAL LOBOTOMY: A SAD CHAPTER IN AMERICAN MEDICAL HISTORY.

Congress wants the Veterans Administration to find and report on World War II vets who underwent lobotomy during and after the war. Flooded with thousands of psychiatric cases in those years, VA physicians lobotomized more than 3,000 patients. Yale-educated neurologist Walter Freeman, the most ardent advocate for lobotomy, was able to sell the procedure to the VA chief, Frank Hines in 1943. He claimed the operation could be done under local anesthesia and did not demand a high degree of surgical skill. By broadly incising neural pathways the patient was reduced to childhood, but that occurred in the best result. Dr. Freeman admitted one-third of patients could not support themselves, and another third were "failures." This surgical loose-cannon brought a hornet's nest down when he used a kitchen icepick inserted through the orbit to cut cranial nerves. In one demonstration the pick broke off in the patient's brain requiring another operation. Many VA surgeons refused to perform lobotomies and were highly critical of Dr. Freeman. He died of cancer in 1974 and might have been mourned by Dr. Mengele. The House Committee on veterans affairs is concerned if the few survivors of this controversial therapy are getting the benefit of modern state-of-the-art medical help.

NO, IT DOESN'T MEAN HE IS A GOOD DOCTOR, BUT IT IS A PRETTY CERTIFICATE.

Legal battles are brewing over board re-certification. In the 1970s the concept of lifetime board certification was set aside and doctors were required to recertify after 10 years. This year the American Board of Internal Medicine is requiring their diplomates to choose from a variety of activities at intervals of two and five years to maintain their certification. The Association of American Physicians and Surgeons has filed an antitrust suit against the American Board of Medical Specialties claiming its program is "a moneymaking self-enrichment scheme" for medical boards. General counsel for the physician's group added that the requirements don't have any proven connection with improving quality of care.

BE CAREFUL WHAT YOU PREDICT, ESPECIALLY ABOUT THE FUTURE.

For the past 15 years, health-care industry analysts have been predicting the decline and eventual disappearance of the self-employed physician. An AMA survey showed 76% of practicing docs were independent in 1983 but the number had dropped to 57% by 1994. It popped back to 61% by 2001, and has remained at 60% in 2012. Accenture studied the issue for two years and predicted the number would reach 36% by 2013. Wrong, and not even close. Moreover, the Idaho Supreme Court ruled St. Luke's Health System's purchase of Saltzer Medical Group, the largest independent group in the state, violated both state and federal anti-trust laws. That decision will surely inhibit larger facilities from absorbing independents.

MR. HOLDER, CAN WE FIX THIS PROBLEM, PLEASE?

Twenty states and the District of Columbia now allow the sale of medical marijuana. Colorado and Washington have made the drug legal for recreational use. The federal government still prohibits the possession, use, and sale of marijuana for any use. As recently as 2005, the US Supreme Court ruled even in states that allow medical marijuana sales, sellers and users can be prosecuted. Eric Holder, Attorney General of the United States, has promised to issue guidelines for marijuana

sellers who are operating in accordance with their state laws. So far, he has failed to do so. At present banks are reluctant to accept large amounts of cash from legitimate marijuana businesses. All of this is wrong. We can't have a law on the books with the Department of Justice looking the other way. A future president could wipe out the industry by strictly enforcing the law. It appears Congress will need to decide whether to keep the national ban or turn the question over to the states.

IN OBSTETRICS BE PREPARED FOR THE UNEXPECTED.

According to attorneys for the plaintiff's family, doctors at Tripler Army Medical Center failed to act promptly when a patient in labor suffered placenta abruptio. An alleged delay in ceasarian section resulted in catastrophic damage to the infant, including cerebral palsy. A settlement of \$9 million was recorded, but that is subject to final approval by the Department of Justice. Pregnancy and delivery are normal natural phenomena, except when they aren't.

ELECTRIC CAR, WHO NEEDS IT?

In Indiana, they sell new for as little as \$600, require no registration, no insurance and no license to operate. Motor scooters have become a very popular way to travel in Evansville. Maximum speed is about 25 mph, but that is fast enough to get to work. Some even drag lawnmowers, canoes, even deer carcasses. They are especially useful for DUI drivers as the only way they have to get to work, earning the nickname liquor cycles. They have sparked a heated political and cultural fight. The mayor said, "it's like someone had taken Miracle-Gro and all of a sudden there are motor scooters everywhere." Previous attempts to pass legislation to tighten scooter laws have failed, but lawmakers believe they have a good chance this session.

IF AT FIRST YOU DON'T SUCCEED...

In Rowan County Kentucky, a 52-year-old man was killed in an explosion. He attempted to light his cigarette while his oxygen supply was operating. He had survived three previous explosions under the same circumstances.

WESTVLETERAN ON TAP? WE CAN'T AFFORD IT.

Considered the holy grail of beers, Westvleteran lager is brewed by Belgian Trappist monks using a centuries-old recipe. They refuse to expand production and sell 60,000 cases per year and no more. Westvleteran is sold only at the monastery gate, by appointment, with a limit of two cases per month at a reasonable price for beer. Of course, resales of the hard-to-get brew go for prices ten times higher or more.

ADDENDA

- At last after years of pleas by the AMA, the dreaded CMS SGR payment formula looks to be near repeal. Still, knowing this congress, don't hold your breath.
- Florence was the first city to have paved streets in 1339 B.C.
- It's okay to laugh in the bedroom, just don't point.
- Be careful whose butt you're kicking today because you may be kissing it tomorrow.
- I think God is going to come down and pull civilization over for speeding.

ALOHA AND KEEP THE FAITH rts

(Editorial comment is strictly that of the writer.)



Service and Value

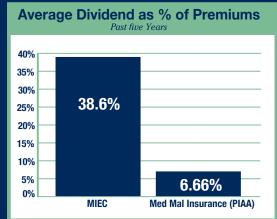
MIEC takes pride in both. For over 30 years, MIEC has been steadfast in our protection of Hawaii physicians. With conscientious Underwriting, excellent Claims management and hands-on Loss Prevention services, we've partnered with policyholders to keep premiums low.

Added value:

- No profit motive and low overhead
- Local claims office in Honolulu
- 17.5 million in dividends* distributed in 2014

For more information or to apply:

- www.miec.com
- Call 800.227.4527
- Email questions to underwriting@miec.com



^{* (}On premiums at \$1/3 million limits. Future dividends cannot be guaranteed.)