Emilie Gorman

From: PAMELA MCCOLL < personal information >
Sent: Tuesday, August 09, 2016 1:03 PM
To: Legislative Services email
Subject: Re: Medical Marijuana - Business input sought from the City of Victoria
Attachments: Aug 9th. document.docx

Here is a discussion paper that is circulating in the international medical community.

You may want to review it and your legal liability carefully as you involve the taxpayers of Victoria in the exposure to the harms related to the use of marijuana for medical or non-medical purposes.

Pamela McColl
The Marijuana Victims' Association Canada

From: "Legislative Services email" <LegislativeServices@victoria.ca>
Sent: Tuesday, August 9, 2016 12:53:44 PM
Subject: Medical Marijuana - Business input sought from the City of Victoria

Good Afternoon,

The City of Victoria is exploring regulations for medical marijuana related businesses operating in Victoria. The purpose of the regulations will be to reduce community impacts while maintaining access to medical marijuana for residents.

On July 28, 2016, staff presented several bylaws to Council that would regulate the business licence and land use aspects of these businesses. The meeting webcast can be viewed here (item #5), and the report can be read here (item #5).

The City welcomes the opportunity to hear from the business community. While extensive consultation has been done on the majority of the proposed regulations, we are looking for feedback specifically on the following items:

- Advertising restrictions for marijuana-related businesses and storefront marijuana retailers which include a maximum of two signs, with alpha-numeric text and no images, and in accordance with the Sign Bylaw

Share your thoughts on the proposed changes by email to legislativeservices@victoria.ca by Monday, August 22, 2016.

The feedback received on the proposed changes will be presented to Council on September 8, 2016, prior to third reading of the Marijuana-Related Business Regulation Bylaw. The community is also invited to speak at the Public Hearing on proposed amendments to the Zoning Regulation Bylaw related to medical marijuana businesses, scheduled for September 8 at 6:30 p.m. at City Hall.

Please be advised that the responses will be made public, in accordance with the *Freedom of Information and Protection of Privacy Act*.

More information, including the proposed regulations, can be found at www.victoria.ca/medicalmarijuana

Sincerely,

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The Marijuana Conundrum in North America

A recognized deficiency: Inadequate protective protocols

An evaluation of risk applied to marijuana products for medical purposes concludes that advanced mitigation strategies and new protective delivery protocols are necessary to adequately protect the public from harm. The Risk Evaluation and Mitigation Strategies (REMS) program is already an approved protocol in the United States (US) by the US Food and Drug Administration and in Canada a similar controlled distribution program is in place including RevAid®.[1,2] These programs are intended to assure patients are monitored to prevent or minimize major side effects and or reactions. There are a number of medications that fall into existing REMS restrictions include thalidomide, clozapine, isotretinoin, and lenilidomide. In both of these programs only prescribers and pharmacists who are registered or patients who are enrolled and who have agreed to meet all the conditions of the program are given access to these drugs.[1,2]

Current Government-approved Cannabinoid Products

Dronabinol (Marinol®, generic), nabilone (Cesamet®, generic) and nabiximols (Sativex®) are synthetic cannabinoid to mimic delta-9-THC and a combination of delta-9-THC and cannabidiol, respectively. They all lack the pesticides, herbicides and fungicides placed on marijuana plants during growth. The longest approved agents, dronabinol and nabilone are indicated for short term use in nausea and vomiting due to chemotherapy and appetite stimulation.[3,4] Long term data does not exist. Nabiximols is used as a buccal spray for multiple sclerosis and as an adjunct for cancer pain.[5] The maximum delta-9-THC strengths available are 10 mg for dronabinol and 2.7 mg/spray of nabiximols.[3,5] Cannabidiol (CBD), a non-psychoactive compound, is one of many cannabinoids found in marijuana. CBD is currently available for free from the U.S. National Institute of Health in government-sponsored clinical trials as potential treatment of resistant seizures (Dravet's Syndrome and Lennox-Gastaut Syndrome).[6]

"Medical" Marijuana products

All marijuana products, including marijuana for medical purposes, fit the prerequisites for a REMS program. The average potency of marijuana more than doubled between 1998 and 2009.[7] In 2015 common leaf marijuana averaged 17.1% THC in Colorado.[8] Examples of oral marijuana products contain 80 mg of THC in chocolates, cookies and drinks and even 420 mg of THC in a "Dank Grasshopper" bar.[9] Butane hash oil (BHO) is a concentrated THC product used in water bongs and/or e- cigarettes and contains upwards of 50 – 90% THC with a Colorado average of 71.7 % THC.[8] One "dab" (280 mg) of 62.1% BHO is equal to 1 gram of 17% THC in marijuana leaf form.[8] These extremely elevated levels of THC make true scientific research with these products incapable of passing Patient Safety Committee standards.[10]

The Thalidomide Parallel

The risks are so severe for thalidomide, in terms of use in pregnancy that a special protocol that educates, evaluates, mitigates and monitors has been made obligatory.[11]

Thalidomide (Contergan®) was developed by a German company, Chemie Gruenenthal, in 1954 and approved for the consumer market in 1957.[12] It was available as an over-the-counter drug for

the relief of "anxiety, insomnia, gastritis, and tension" and later it was used to alleviate nausea and to help with morning sickness by pregnant women. Thalidomide was present in at least 46 countries under a variety of brand names and was available in "sample tablet form" in Canada by 1959 and licensed for prescription on December 2, 1961. Although thalidomide was withdrawn from the market in West Germany and the UK by December 2, 1961, it remained legally available in Canada until March of 1962. It was still available in some Canadian pharmacies until mid-May of 1962.[12]

Canada had permitted the drug onto the Canadian market when many warnings were already available

An association was being made in 1958 of phocomelia (limb malformation) in babies of mother's using thalidomide. A trial conducted in Germany against Gruenenthal, for causing intentional and negligent bodily injury and death, began in 1968 ending in 1970 with a claim of insufficient evidence. Later, the victims and Gruenenthal settled the case for 100 million dollars.[11]

In 1962 the American pharmaceutical laws were increased by the *Kefauver-Harris Drug Amendment* of 1962 and proof for the therapeutic efficiency through suitable and controlled studies would be required for any government approved medication.[13] According to paragraph 25 of the Contergan foundation law, every 2 years a new report is required to determine if further development of these regulations are necessary.[13]

In 1987 the War Amputations of Canada established The Thalidomide Task Force, to seek compensation for Canadian-born thalidomide victims from the government of Canada.[12]

In 1991, the Ministry of National Health and Welfare (the current Health Canada) awarded Canadian-born thalidomide survivors a small lump-sum payment.[12]

In 2015 the Canadian government agreed on a settlement of $180 million dollars to 100 survivors of thalidomide drug exposure and damage.[14] Through Rona Ambrose, in her capacity as the Health Minister for the government of Canada at the time of the negotiations, an attempt was made to involve the drug companies related to the thalidomide issue in the survivor's settlement agreement. Negotiations with the drug companies failed. The Canadian taxpayer alone paid to amend the survivors by way of monetary award.

Thalidomide continues to be sold under the brand name of Immunoprin®, among others in a REMS program. It is an immunomodulatory drug and today, it is used mainly as a treatment of certain cancers (multiple myeloma) and leprosy.[11]

Question: If the drug thalidomide included psychotropic properties and offered the "high" of marijuana would it be prudent or responsible to allow it to be legally sold and marketed for non-medical purposes - acknowledging thalidomide's record for toxicity in pregnancy?

Marijuana Risk Assessment and Government Acknowledgement

Risks demonstrated in the scientific literature include genetic and chromosomal damage.[15, 16]

When exposure occurs in utero, there is an association with many congenital abnormalities including cardiac septal defects, anotia, anophthalmos, and gastroschisis. Marijuana use can disrupt foetal growth and the development of organs and limbs and may result in mutagenic alterations in DNA. Cannabis has also been associated with foetal abnormalities in many studies including low birth weight, foetal growth restriction, preterm birth spontaneous miscarriage, spina bifida and others.[15]

Phocomelia has been shown in testing in a similar preclinical model (hamster) to that which revealed the teratogenicity of thalidomide.[15]

THC has the ability to interfere with the first stages in the formation of the brain of the fetus; this event occurs two weeks after conception. Exposure to today's high potency marijuana in early pregnancy is associated with anencephaly, a devastating birth defect in which infants are born with large parts of the brain or skull missing.[15]

The existence of specific health risks associated with marijuana products are acknowledged by national and various local governments and a plethora of elected officials in both Canada and the United States.[16, 17, 18]

Warnings and the contraindications for use by specific populations and in association with identified conditions, have been publicized by the Federal Government of Canada and the Federal Government of the United States of America through their respective health agencies.[16, 17, 18]

A government of Canada leaflet produced by Health Canada and updated in December 2015: Consumer Information – Cannabis (Marihuana, marijuana) reads[19]:

"The use of this product involves risks to health, some of which may not be known or fully understood. Studies supporting the safety and efficacy of cannabis for therapeutic purposes are limited and do not meet the standard required by the Food and Drug Regulations for marketed drugs in Canada."[19]

"Using cannabis or any cannabis product can impair your concentration, your ability to think and make decisions, and your reaction time and coordination. This can affect your motor skills, including your ability to drive. It can also increase anxiety and cause panic attacks, and in some cases cause paranoia and hallucinations."[19]

"When the product should not be used: under the age of 25, are allergic to any cannabinoid or to smoke, have serious liver, kidney, heart or lung disease, have a personal or family history of serious mental disorders such as schizophrenia, psychosis, depression, or bipolar disorder, are pregnant, are planning to get pregnant, or are breast-feeding, are a man who wishes to start a family, have a history of alcohol or drug abuse or substance dependence."[19]

"A list of health outcomes related to long term use includes the following:

Increased risk of triggering or aggravating psychiatric and/or mood disorders (schizophrenia, psychosis, anxiety, depression, bipolar disorder), decrease sperm count, concentration and motility, and increase abnormal sperm morphology. Negatively impact the behavioural and cognitive development of children born to mothers who used cannabis during pregnancy."[19]

In Canada, the College of Family Physicians has issued guidelines for issuing marijuana prescriptions.[20]

"Dried cannabis is not appropriate for patients who: a) Are under the age of 25 (Level II) b) Have a personal history or strong family history of psychosis (Level II) c) Have a current or past cannabis use disorder (Level III) d) Have an active substance use disorder (Level III) e) Have cardiovascular disease (angina, peripheral vascular disease, cerebrovascular disease, arrhythmias) (Level III) f) Have respiratory disease (Level III) or g) Are pregnant, planning to become pregnant, or breastfeeding (Level II)"[20]

"Dried cannabis should be authorized with caution in those patients who: a) Have a concurrent active mood or anxiety disorder (Level II) b) Smoke tobacco (Level II) c) Have risk factors for cardiovascular disease (Level III) or d) Are heavy users of alcohol or taking high doses of opioids or benzodiazepines or other sedating medications prescribed or available over the counter (Level III)"[20]

In February 2013 The College of Family Physicians of Canada issued a statement advancing the position that physicians should sign a declaration rather than write a prescription as the potential liability, as well as the ethical obligations, for health professionals prescribing marijuana for medical purposes appears not to have been adequately addressed by Health Canada. [21]

"In our view, Health Canada places physicians in an unfair, untenable and to a certain extent unethical position by requiring them to prescribe cannabis in order for patients to obtain it legally. If the patient suffers a cannabis-related harm, physicians can be held liable, just as they are with other prescribed medications. Physicians cannot be expected to prescribe a drug without the safeguards in place as for other medications – solid evidence supporting the effectiveness and safety of the medication, and a clear set of indications, dosing guidelines and precautions."[21]

Representatives of the government of the United States held a press conference at the Office of National Drug Policy (ONDCP) in 2005. Mental health experts and scientists joined high-ranking government officials to discuss an emerging body of research that identified clear links between marijuana use and mental health disorders, including depression, suicidal thoughts and schizophrenia.[22]

The US Substance Abuse and Mental Health Service Administration (SAMHSA) report about the correlation between age of first marijuana use and serious mental illness; and an open letter to parents on "Marijuana and Your Teen's Mental Health," signed by twelve of the Nation's leading mental health organizations, ran in major newspapers and newsweeklies across the country.[23]

Included were the following announcements:

"Regular use of the drug has appeared to double the risk of developing a psychotic episode or long-term schizophrenia."[23]

"Research has strongly suggested that there is a clear link between early cannabis use and later mental health problems in those with a genetic vulnerability - and that there is a particular issue with the use of cannabis by adolescents."[23]

"Adolescents who used cannabis daily were five times more likely to develop depression and anxiety in later life."[23]

In 2016 the Obama Administration steadfastly opposes legalization of marijuana and other drugs because legalization would increase the availability and use of illicit drugs, and pose significant health and safety risks to all Americans, particularly young people.[24] The US government still maintains marijuana is classified as a Schedule I drug, meaning it has a high potential for abuse and no currently accepted medical use in treatment in the United States.[17, 18]

Risk Evaluation and Mitigation Strategy for Marijuana Products

The dispensing of marijuana for medical purposes must follow a strict dispensing and monitoring protocol; no less arduous than that used for the delivery of drugs such as thalidomide.

Recommendation - The implementation of a REMS for marijuana products (REMSMP).

1. The first order for a government is to protect the public. As such, it befits a government approving marijuana for medical purposes to implement a REMS program.

2. Medical cannabis/marijuana dispensaries/stores/delivery systems will be required to comply with all necessary components of a rigorous REMS program prior to selling and dispensing marijuana products.

3. Governmental regulatory organizations must be responsible for the cannabis/marijuana for medical purposes programs and obtain the required evaluations [(i.e. laboratory tests (pregnancy, HCG, etc.), physical and mental health examination documentation], signed patient consent, provider contract and education forms - performed in the required time frames both before initiation, during and after continued usage of marijuana products for medical purposes.

4. Quarterly audits will be performed, by the government regulatory organization, on each medical marijuana/cannabis dispensary for compliance. Failure to comply with the REMSMP program will result in fines and other appropriate penalties to the marijuana dispensaries.

A REMS for Marijuana Product Potential Framework:

EMBRYO-FETAL TOXICITY & BREASTFEEDING

- Marijuana causes DNA damage in male and female patients.[15] If marijuana is used during conception or during pregnancy, it may cause birth defects, cancer formation in the offspring, Downs Syndrome or embryo-fetal death.[15, 16, 18]
- Pregnancy must be ruled out before the start of marijuana treatment. Pregnancy must be prevented by both the male and female patients during marijuana treatment by the use of two reliable methods of contraception.
- When there is no satisfactory alternative treatment, females of reproductive potential may be treated with marijuana provided adequate precautions are taken to avoid pregnancy.
- Females of Reproductive Potential: Must avoid pregnancy for at least 4 weeks before beginning marijuana therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Females must commit to either abstain continuously from heterosexual intercourse or use two methods or reliable birth control as mentioned. They must have two negative pregnancy tests prior to initiating marijuana therapy and monthly pregnancy test with normal menses or two months with abnormal menses and for at least 1 month after stopping marijuana therapy.
- Males (all ages): DNA damage from marijuana is present in the semen of patients receiving marijuana.[15] Therefore, males must always use a latex or synthetic condom during any sexual contacts with females of reproductive potential while using marijuana and for up to at least 28 days after discontinuing marijuana therapy, even if they have undergone a successful vasectomy. Male patients using marijuana may not donate sperm.
- Blood Donation: Patients must not donate blood during treatment with marijuana and for at least 1 month following discontinuation of marijuana because the blood might be given to a pregnant female patient whose fetus should not be exposed to marijuana.
- Marijuana taken by any route of administration may result in drug-associated DNA damage resulting in embryo-fetal toxicity. Females of reproductive potential should avoid contact with marijuana through cutaneous absorption, smoke inhalation or orally.
- If there is contact with marijuana products topically, the exposed area should be washed with soap and water.
- If healthcare providers or other care givers are exposed to body fluids of a person on marijuana, the exposed area should be washed with soap and water. Appropriate universal precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to marijuana.
- Several psychoactive cannabinoids in marijuana are fat soluble and are found to concentrate in breast milk. Nursing mothers must not be receiving marijuana.[16] Consult the primary care provider about how long to be off of marijuana before considering breast feeding.

NON-SEMINOMA TESTICULAR GERM CELL CARCINOMA

- Marijuana use is a known risk factor in the development of non-seminoma testicular germ cell carcinoma in males.[25 - 28]
- The presence of non-seminoma testicular germ cell carcinoma must be excluded before the start of marijuana treatment. The patient's primary care provider must perform a testicular examination and review the patient's human chorionic gonadotropin (HCG) blood test

before starting marijuana. Male patients must perform weekly testicular self-evaluations while receiving marijuana. They are also required to have their primary care provider perform a testicular evaluation and a HCG blood test performed every 4 months while receiving marijuana.[29, 30]

MENTAL HEALTH:

- Short term high dose and chronic marijuana usage is a known risk factor for the development of multiple mental health disorders.[16, 18, 20, 31 - 34] Depression, paranoia, mental confusion, anxiety, addiction and suicide potential are all associated with acute and chronic exposure to marijuana.[16, 18] Decline in intelligence is a potential risk of adolescent-onset marijuana exposure.[16, 18, 35]

The presence of these mental health disorders must be evaluated by a licensed psychiatrist or psychologist by use of the Mini International Neuropsychiatric Interview or equivalent validated diagnostic instrument before marijuana is started. The diagnostic mental health evaluation tool will be completed every 1month by an independent licensed psychiatrist or psychologist for a minimum of 6 months until unchanging and then every 4 months thereafter while receiving marijuana ending 4 months after the last exposure to marijuana.[36]

PSYCHIATRIC EVALUATIONS:

History of Substance Abuse Disorder: As the prevalence of substance use disorders amongst those patients requesting medical authorization of marijuana products is known to be extremely high the patient population must be screened prior to dispensing marijuana products for risk of a substance use disorder. Substance use must be monitored prior to onset of marijuana with the World Health Organization, Smoking and Substance Involvement Screening Test (WHO-ASSIST, V3.0), and repeated at monthly intervals until unchanging and every 3 months thereafter while receiving marijuana, ending 6 months after the last exposure to marijuana.[37]

Conclusion

The evidence that thalidomide and tobacco products were harmful was known to the manufacturers/distributors before government and the populous acknowledged these dangers. To date, there continue to be legal repercussions to said manufacturers/distributors/government for knowingly placing the public at risk. We believe that the same will happen for marijuana products and that it is our responsibility to assist the Canadian government to protect the public from a similar outcome. Since the government is fully aware of the marijuana harms, the government must not be complicit in risking Canadian health/lives, but rather must mitigate any and all such risk to current and future generations.[38, 39] The REMSMP program described assists in providing patient education, provider education and required patient monitoring before any marijuana products are allowed to be dispensed. The program also requires on-going data collection and analysis, to determine the actual hazards from marijuana use and whether the program should even continue. As the stewards of the country's human and financial resources, it is critical that government protect the public from potential irreversible harm and itself from litigation risk by

harmed individuals knowing that, in the context of marijuana use, harm is not only possible but probable.

Endorsements

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Emilie Gorman

From: PAMELA MCCOLL personal information >
Sent: Tuesday, August 09, 2016 1:05 PM
To: Legislative Services email
Cc: personal information
Subject: Fwd: Ottawa should warn Canadians about the risks of marijuana

- *9 Aug 2016*
- *The Vancouver Sun*

Ottawa should warn Canadians about the risks of marijuana

The online discussion paper in which the Canadian government outlines its rationale for the legalization of marijuana for non-medical purposes fails to offer Canadians critical scientific findings including that phocomelia (malformation of limbs) has been shown in testing in a similar preclinical model to that which revealed the teratogenicity of thalidomide.

A Health Canada document lists a plethora of risks, and cites 1,000 references that substantiate claims of harm. A condensed consumer version of this document is required by Health Canada to be sent out with all legally obtained marijuana through the legal MMPR licensees. Of special note is a warning that men planning on starting a family should not use marijuana for medical purposes. This warning is not shared in the public consultation document.

Since the government is fully aware of the marijuana harms, it must not be complicit in risking the health of the public. It is critical that the government protect itself from litigation risk by informing individuals that harm is not only possible but probable.

Pamela McColl, The Marijuana Victims' Association, Vancouver

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From: PAMELA MCCOLL personal information >
Sent: Tuesday, August 09, 2016 4:49 PM
To: Legislative Services email
Subject: Fwd: articles
Attachments: MJ for Pain Relief J of Pain letter to Editor critique Oct 2013.pdf; Genome wide Assoc study of cannabis depend 2016 Sherva.pdf; Impact MJ Dispens on ABuse Depend 2015 Mair Drug Alco Depend.pdf; Med Board Expectns for Physic Recommending MJ JAMA 2016.pdf

Reference materials submitted to the City of Victoria who are exploring the idea of involving itself in Canadian drug policy.

Pamela McColl
The Marijuana Victims' Association

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
ELSEVIER

The Journal of Pain, Vol 14, No 10 (October), 2013: pp 1250-1251
Available online at www.jpain.org and www.sciencedirect.com

Letters to the Editor

Marijuana for Pain Relief: Don't Jump to Conclusions

To the Editor:

The title of Wilsey et al's recent study "Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain"[24] piqued our interest, as did the abstract that compared the calculated numbers-needed-to-treat of 2.9 to 3.2 favorably to "traditional neuropathic pain medications." The abstract describes minimal psychoactive effects and deems the overall results as "a clinically significant outcome." Unfortunately, these conclusions are not borne out by careful examination of this study and contrasting it with other available treatments.

The study involves inhaling cannabis vapor (2 concentrations) or placebo vapor under a hood (4 puffs) and then a second treatment 120 minutes later of 4 to 8 puffs. Outcomes are assessed up to 300 minutes after baseline measurements, which is 240 minutes after initial treatment. The subjects were exposed to all 3 treatments separated by a minimum of 3 days to allow adequate recovery. There was significant reduction in pain following the inhalation of both concentrations of cannabis vapor. All subjects had neuropathic pain (including complex regional pain syndrome) with a median duration of 9 years of symptoms.

This study accurately represents pilot, preliminary data suggestive of a potential beneficial effect. However, it is clear that vaporized cannabis lacks sufficient data to be compared in any way to "traditional neuropathic medications." When the authors make such a comparison to standard treatments, they must provide evidence that they are comparing apples to apples. Without even looking at the literature, many problems with the authors' overreaching conclusions are evident.

First, many treatments have initial effects that are not sustained. For subjects with 9 years of pain, how meaningful is pain relief 240 minutes after administering a treatment? Does the effect persist for a day, a week, a month, or 9 years? Does it provide around-the-clock relief? How many times a day must a person administer the cannabis to provide consistent relief? If cognitive effects reportedly diminish with chronic use, does a tolerance to the analgesic effects also develop over time? Are there any other salutary effects that appear or disappear over time? Are there any placebo controlled data of comparable duration to the typical pharmaceutical trial (4–12 weeks)?

Second, how does this laboratory experiment translate to real-life treatment? For a pill or capsule, patients can store the medication in a secure medicine cabinet and take it in essentially any setting. How does use under a hood of a carefully prepared vapor translate to home, work, or public use?

Third, function is becoming an increasingly important outcome measure for pain treatment studies. The subjects in this study were preselected to have had previous cannabis exposure to "reduce the risk of adverse psychoactive effects in naive individuals," a requirement that is typically not required in other pain treatment efficacy studies and degrades the quality of the reported adverse effects. Additionally, all participants were "accompanied home by a responsible adult," experienced a significant dose effect for "bad drug effect," and cannabis produced a "general cognitive decline as indicated by the difference of scores between treatment groups on all tests over time." Would these effects lessen, worsen, or remain the same over time? Would repeated dosing lead to more impact on function and cognition? It would appear that cognition and the ability to drive are important functional correlates of a favorable clinical outcome. The authors' conclusion is that the effect sizes seen with learning and memory are "unlikely to have significant impact on daily functioning," but is this supported by research? The reassurances that nonprospective data for recreational and "medical" users of marijuana reveals fewer negative effects with chronic use falls short of answering these questions. The U.S. Food and Drug Administration wouldn't allow such data to fill in for prospective data. For the noncontrolled studies, how aware are the patients of the cognitive impairment? Is the patient the best judge of any impairment?

Fourth, for most medications, there is an established therapeutic window, meaning a dose range that is associated with a clinically meaningful response with minimal or controlled adverse effects. What is that window for cannabis? How easy is it for a person to exceed the minimum analgesic dose and end up with more cognitive effects? The researchers were not even able to report on the actual amount of cannabis each patient consumed in the study, aside from numbers of puffs.

None of the authors has any institutional or personal conflicts of interest. Address reprint requests to Brett R. Stacey, MD, Oregon Health & Science University, Comprehensive Pain Center, CH4P, 3303 SW Bond Ave, Portland, OR 97239. E-mail: staceyb@ohsu.edu

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Finally, a quick review of the literature reveals many areas of controversy: mental illness correlates with cannabis use,[4,10,14,15,18] impairment of driving ability,[1,2,6,8,9,13,22,23] cannabis use associated with drugs of abuse,[16,19,21] impacts on work,[12] and other health issues associated with cannabis.[4,5,7,11,17,20] Cannabis isn't just another experimental medication or treatment.[3] It has a cultural and scientific context that is unique in our society, and new data are needed to move beyond emotional-based discussions. The burden on researchers to publish valid conclusions is high and was not met in this study.

Sincerely,

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Original Investigation

Genome-wide Association Study of Cannabis Dependence Severity, Novel Risk Variants, and Shared Genetic Risks

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IMPORTANCE Cannabis dependence (CAD) is a serious problem worldwide and is of growing importance in the United States because cannabis is increasingly available legally. Although genetic factors contribute substantially to CAD risk, at present no well-established specific genetic risk factors for CAD have been elucidated.

OBJECTIVE To report findings for *DSM-IV* CAD criteria from association analyses performed in large cohorts of African American and European American participants from 3 studies of substance use disorder genetics.

DESIGN, SETTING, AND PARTICIPANTS This genome-wide association study for *DSM-IV* CAD criterion count was performed in 3 independent substance dependence cohorts (the Yale-Penn Study, Study of Addiction: Genetics and Environment [SAGE], and International Consortium on the Genetics of Heroin Dependence [ICGHD]). A referral sample and volunteers recruited in the community and from substance abuse treatment centers included 6000 African American and 8754 European American participants, including some from small families. Participants from the Yale-Penn Study were recruited from 2000 to 2013. Data were collected for the SAGE trial from 1990 to 2007 and for the ICGHD from 2004 to 2009. Data were analyzed from January 2, 2013, to November 9, 2015.

MAIN OUTCOMES AND MEASURES Criterion count for *DSM-IV* CAD.

RESULTS Among the 14 754 participants, 7879 were male, 6875 were female, and the mean (SD) age was 39.2 (10.2) years. Three independent regions with genome-wide significant single-nucleotide polymorphism associations were identified, considering the largest possible sample. These included rs14324-1591 (β = 0.54, $P = 4.32 \times 10^{-10}$ for the meta-analysis) in novel antisense transcript *RP11-206M11.7*; rs146091982 (β = 0.54, $P = 1.33 \times 10^{-9}$ for the meta-analysis) in the solute carrier family 35 member G1 gene (*SLC35G1*); and rs77378271 (β = 0.29, $P = 2.13 \times 10^{-8}$ for the meta-analysis) in the CUB and Sushi multiple domains 1 gene (*CSMD1*). Also noted was evidence of genome-level pleiotropy between CAD and major depressive disorder and for an association with single-nucleotide polymorphisms in genes associated with schizophrenia risk. Several of the genes identified have functions related to neuronal calcium homeostasis or central nervous system development.

CONCLUSIONS AND RELEVANCE These results are the first, to our knowledge, to identify specific CAD risk alleles and potential genetic factors contributing to the comorbidity of CAD with major depression and schizophrenia.

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After nicotine, cannabis is the most widely abused drug worldwide.[1] In the United States, the accelerated decriminalization of cannabis is based on the erroneous perception that it is relatively harmless.[2] In fact, cannabis use produces craving,[3] dependence,[4] and drug-seeking behavior,[5] as with the use of other substances. Despite these risks, the prevalence of cannabis use and cannabis use disorders has dramatically increased since 2001,[6] and the political momentum to increase availability has continued. Use of cannabis early in life is associated with an increased risk for schizophrenia (SCZ),[7] and sets of SCZ-associated risk alleles predict cannabis use.[8] Cannabis use is also a risk factor for depressive symptoms,[9] and a twin study showed cannabis dependence (CAD) to be associated with an elevated risk for major depressive disorder (MDD).[10] Substance use and other psychiatric illnesses may share common genetic risk factors; or reverse causation, self-medication, or confounding by other factors may explain their co-occurrence.

Despite knowledge of the neurobiology of the endocannabinoid system and its response to tetrahydrocannabinol, little is known about specific genetic factors influencing susceptibility to CAD or cannabis abuse. A twin study showed that several aspects of cannabis use are heritable, including an early opportunity to use (h^2 = 72%), early onset of use (h^2 = 80%), lifetime use of cannabis 11 or more times (h^2 = 76%), and cannabis abuse or dependence (h^2 = 21%-72%), where h^2 is heritability.[11-13] Possible evidence of linkage of CAD on chromosome 16[14] and linkage and association encompassing the neuregulin 1 gene (*NRG1* [OMIM 142445]; known as a possible SCZ risk gene[15]) on chromosome 8[16] have been found. Despite several genome-wide association studies (GWAS) on cannabis-related traits, no genome-wide significant (GWS) associations were observed for initiation of use[17] or for CAD.[18] Herein we report on findings for *DSM-IV* CAD criteria from association analyses performed in large cohorts of African American and European American participants from 3 studies of substance use disorder genetics who underwent genotyping with genome-wide microarrays. The primary cohort has been used in previous studies to identify genes associated with opioid (OD),[19] cocaine (CD),[20] alcohol (AD),[21] and nicotine (ND) dependence[22] and posttraumatic stress disorder.[23]

Key Points

Question What specific genetic variants contribute to cannabis dependence risk?

Findings Three regions had genome-wide significant evidence of association with cannabis dependence and evidence of genetic overlap between cannabis dependence and schizophrenia and major depressive disorder

Meaning Cannabis dependence has a genetic risk component that may overlap with other psychiatric disorders.

Methods

Participants and Diagnostic Procedures

The samples included 6000 African American and 8754 European American participants (race was assigned based on genetic data; eMethods in the Supplement) from the following 3 studies: (1) the Yale-Penn Study cohort of small nuclear families and unrelated individuals (2020 individuals in 850 families and 6951 unrelated individuals), collected to study the genetics of substance dependence[19-21]; (2) the GWAS data set from the Study of Addiction: Genetics and Environment (SAGE),[24-27] collected to study the genetics of AD, ND, and CD (183 individuals in 89 families and 3707 unrelated individuals); and (3) the GWAS International Consortium on the Genetics of Heroin Dependence (ICGHD),[28,29] a collaboration formed to identify genes associated with heroin dependence risk (66 individuals in 33 families and 1827 unrelated individuals). The SAGE and ICGHD data sets are publicly available via application. The present study received institutional review board approval from all participating institutions, and written informed consent was obtained from all study participants.

Participants from the Yale-Penn Study were recruited from 2000 to 2013. These participants were administered the Semi-Structured Assessment for Drug Dependence and Alcoholism[30] to derive *DSM-IV* diagnoses of lifetime CAD and other major psychiatric traits. Data were collected for the SAGE trial from 1990 to 2007, and participants underwent phenotyping with the Semi-Structured Assessment for the Genetics of Alcoholism.[31] Data were collected for the ICGHD from 2004 to 2009, and participants completed a comprehensive psychiatric diagnostic interview based on the Semi-Structured Assessment of the Genetics of Alcoholism-Australia.[31] The method of phenotyping was similar across the 3 samples. Additional information about recruitment, genotyping, imputation, and quality control for the study cohorts is provided in eMethods in the Supplement.

Statistical Analysis

Data were analyzed from January 2, 2013, to November 9, 2015. Association analyses were performed using a count of *DSM-IV* CAD criteria (0-7) as the outcome variable and the imputed minor allele dosage (adjusted for sex, age, and the first 3 ancestry principal components) as a predictor variable. This ordinal trait model has greater power to detect genetic associations than a univariate model based on disease status because of greater information content and improved specificity of the dependence measure. Association tests were performed using linear association models embedded in generalized estimating equations to correct for correlations among related individuals.[32] Analyses were performed separately within each data set and population group, and the results were combined by meta-analysis using the inverse variance method implemented in the program METAL.[33] Genomic inflation factors (λ) were calculated within each subpopulation, and *P* values were corrected accordingly. We performed a second correction for the λ factor calculated after the meta-analysis.

For the primary analysis, individuals were included regardless of cannabis exposure. As secondary analyses, individuals who reported never having used cannabis were excluded, and the primary model was repeated adjusting for the

Table 1. Demographic Characteristics of the Study Cohorts

Sample[a]	Age, Mean (SD), y	Female Sex, No./Total No.	*DSM-IV* CAD Criterion Count, Mean (SD)	CAD Diagnosis, No./Total No. of Participants	Correlation With *DSM-IV* CAD Criterion Count, r^2			
					AD	CD	ND	OD
Yale-Penn African American	41.3 (9.7)	2209/4750	1.7 (2.2)	1296/4750	0.40	0.30	0.36	0.15
Yale-Penn European American	38.6 (11.5)	1712/4221	2.0 (2.3)	1388/4221	0.27	0.32	0.31	0.23
SAGE African American	39.9 (7.3)	638/1250	1.4 (2.2)	276/1250	0.43	0.43	0.39	0.17
SAGE European American	38.4 (9.7)	1478/2640	1.0 (1.9)	434/2640	0.51	0.61	0.40	0.41
ICGHD	36.2 (9.1)	838/1893	3.2 (2.5)	1062/1893	0.24	0.24	0.25	0.33

Abbreviations: AD, alcohol dependence; CAD, cannabis dependence; CD, cocaine dependence; ICGHD, International Consortium on the Genetics of Heroin Dependence; ND, nicotine dependence; OD, opioid dependence; SAGE, Study of Addiction: Genetics and Environment.

[a] Samples are described in the Participants and Diagnostic Procedure subsection of the Methods section.

criterion counts for AD, CD, and OD. Participants from 2 genotyping batches in the Yale-Penn cohort (Yale-Penn 1 and Yale-Penn 2) were combined with the SAGE sample to form a discovery data set. A sample consisting of the ICGHD data and additional samples from the Yale-Penn cohort who did not undergo genotyping at the time of the discovery analyses (Yale-Penn 3) were used to replicate the top associations.

Cross-Disorder Analyses

We attempted to uncover shared genetic variation between CAD and 5 psychiatric disorders, including SCZ, MDD, bipolar affective disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder using the GWAS analysis reported herein and publicly available GWAS results from the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc).[14] To explore cross-disorder genetic relationships, we used stratified quintile-quintile (QQ) plots to evaluate the relative enrichment of single-nucleotide polymorphisms (SNPs) associated with both disorders. The QQ plots, which contrast the observed distribution of *P* values with the expected distribution under the null hypothesis (uniform in GWAS), were used to assess *P* value inflation in the GWAS results. Grouping associated SNPs for one disorder and comparing (across groups) the QQ plots of another disorder, however, could also reveal the enrichment of GWAS signals between disorders, which made them suitable for cross-disorder enrichment screening.

We also applied a statistical framework for pleiotropy analysis, Genetic Analysis Incorporating Pleiotropy and Annotation (GPA).[15] The GPA was built as a mixture model with parameters estimated using an efficient expectation-maximization algorithm, where associated SNPs were modeled with a $\beta[\alpha, 1]$ distribution and unassociated SNPs with a uniform [0, 1] distribution. A likelihood ratio test assessed the significance of pleiotropy between disorders. The GPA also detected the SNPs that were pleiotropic by calculating the posterior probability of association with both disorders.

Results

Participant demographic characteristics and the correlation between the criterion counts for CAD and other substance use disorder traits are shown in Table 1. The *DSM-IV* CAD criterion counts were significantly ($P < .05$) correlated with the criteria counts for AD, CD, OD, and ND. The correlations varied by sample and population and ranged from $r^2 = 0.15$ for OD to $r^2 = 0.61$ for CD criteria. The CAD criterion counts were significantly heritable in European American (19%-25%; $P = .006$) but not African American (10%-11%; $P = .08$) participants. eFigure 1 in the Supplement shows a histogram of the CAD criterion count in African American and European American participants in each cohort; 3 or more criteria indicate a diagnosis of CAD. The criterion count distribution is very similar in African American and European American participants. In the Yale-Penn sample, where comorbid psychiatric diagnoses were available, CAD was significantly associated with MDD in African American participants (odds ratio, 1.07; $P = .006$) but not SCZ, bipolar affective disorder, attention-deficit/hyperactivity disorder, or autism spectrum disorder. Cannabis dependence was not associated with any of these disorders in European American participants.

GWAS Results

Manhattan and QQ plots for the meta-analysis discovery GWAS results for African American and European American Yale-Penn 1 and 2 and SAGE cohorts are displayed in eFigures 2 and 3 in the Supplement. We found little evidence of *P* value inflation. Table 2 shows associations in the discovery sample with $P < 1.0 \times 10^{-5}$ in African American or European American participants or the combined meta-analysis, trimmed for linkage disequilibrium. eTable 1 in the Supplement shows the same results, together with additional information about each SNP, including the results within each discovery sample subgroup, after excluding individuals with no cannabis exposure, and after adjusting for comorbid substance use disorders. We identified GWS associations with reliably imputed SNPs in 3 distinct regions (Table 2), 2 specific to African American participants and 1 in the combined sample. First, rs186825689 ($P = 1.86 \times 10^{-8}$ for the African American meta-analysis) is located 12.4 kb upstream from the gene encoding S100 calcium binding protein (*S100B*) with contributions from both informative African American samples. Second, rs113445941 ($P = 2.18 \times 10^{-8}$ for the African American meta-analysis) maps to a novel antisense transcript *RP11-206M11.7* (Havana gene: OTTHUMG00000159583) located in the gene of the same name on chromosome 3 with at least nominally significant evidence in each of the 3 African American samples. Third, rs77578171 ($P = 2.76 \times 10^{-8}$ for the European American meta-analysis) is an intronic SNP in the CUB

Table 2. SNPs Associated With *DSM-IV* CAD at $P < 1.0 \times 10^{-5}$ in the Discovery Meta-analysis Trimmed for SNPs in Linkage Disequilibrium

Chromosome	Base Pair Position[a]	Effect Allele	Reference Allele	SNP	Gene	Effect Allele Frequency		P Value for Meta-analysis		
						African American Cohort	European American Cohort	African American Cohort	European American Cohort	All Participants
1	88729683	C	T	rs74823926	NA	0.96	0.97	5.26×10^{-7}	6.36×10^{-1}	1.40×10^{-5}
2	39166173	T	G	rs114383460	*ARHGEF33*	0.96	NA	1.09×10^{-6}	NA	NA
2	78028838	T	A	rs12621150	NA	0.85	0.90	7.67×10^{-1}	1.05×10^{-6}	2.91×10^{-4}
2	100451676	T	C	rs7586604	*AFF3*	0.39	0.16	4.15×10^{-5}	6.19×10^{-3}	1.06×10^{-6}
2	103764414	G	A	rs144605126	NA	0.96	NA	8.67×10^{-7}	NA	NA
2	118490901	G	A	rs150064803	NA	0.95	NA	3.41×10^{-7}	NA	NA
2	167214714	G	A	rs143020225	*SCN9A*	0.95	NA	7.19×10^{-7}	NA	NA
3	149013935	G	A	rs143244591[b]	*RP11-206M11.7*	0.96	NA	2.18×10^{-8}[b]	NA	NA
4	25201318	A	T	rs73252553	*PI4K2B*	0.96	0.90	1.18×10^{-1}	2.28×10^{-5}	1.66×10^{-7}
4	119716950	A	C	rs28595532	*SEC24D*	0.92	0.94	2.02×10^{-7}	1.08E-01	1.13×10^{-6}
5	11892384	T	C	rs114311699	*CTNND2*	0.96	NA	3.78×10^{-7}	NA	NA
5	177746600	G	C	rs10066744	*COL23A1*	0.96	NA	4.82×10^{-7}	NA	NA
6	51221457	A	G	rs17665889	NA	0.94	0.90	1.51×10^{-1}	9.41×10^{-8}	2.58×10^{-4}
7	84952631	A	G	rs12534830	NA	0.88	0.66	7.76×10^{-1}	1.54×10^{-5}	4.52×10^{-7}
8	3073489	A	G	rs77378271[b]	*CSMD1*	0.96	0.94	2.13×10^{-1}	2.76×10^{-8}[b]	4.60×10^{-8}[b]
9	29364327	G	T	rs10969106	NA	NA	0.97	NA	7.39×10^{-8}	NA
10	31981385	T	C	rs115553536	NA	0.94	NA	6.46×10^{-7}	NA	NA
10	43592809	G	C	rs74400468	*RET*	0.96	0.97	5.53×10^{-2}	1.59×10^{-6}	6.46×10^{-7}
10	70490106	A	T	rs12218439	*CCAR1*	0.96	0.96	1.01×10^{-6}	2.01×10^{-1}	1.13×10^{-4}
10	95659958	A	G	rs146091982	*SLC35G1*	0.95	NA	1.95×10^{-7}	NA	NA
11	20561010	C	G	rs73443003	NA	0.75	NA	1.31×10^{-6}	NA	NA
11	81433204	A	AAAG	rs200453611	NA	0.91	0.84	9.43×10^{-7}	6.24×10^{-1}	6.81×10^{-4}
11	108899423	GTA	G	rs200391037	NA	0.96	0.88	1.02×10^{-1}	3.72×10^{-6}	1.32×10^{-6}
12	56274155	T	C	rs193047854	NA	0.97	NA	7.06×10^{-7}	NA	NA
20	21706604	A	AT	rs199783889	NA	0.94	NA	3.32×10^{-7}	NA	NA
21	18019319	T	C	rs78068107	NA	0.96	NA	1.02×10^{-6}	NA	NA
21	48006053	A	C	rs186825689[b]	NA	0.96	NA	1.86×10^{-8}[b]	NA	NA

Abbreviations: CAD, cannabis dependence; NA, not applicable; SNP, single-nucleotide polymorphism.

[a] Indicates in human genome assembly build 37.

[b] Indicates genome-wide significant SNPs and *P* values.

and Sushi multiple domains 1 gene (*CSMD1* [OMIM 608397]) with evidence of association in 3 of the 6 samples. We also identified consistent, non-GWS evidence of association in the combined sample of European American and African American participants with a large block of SNPs in and around the phosphatidylinositol 4-kinase type 2β gene (*PI4K2B* [OMIM 612101]), with consistent effect direction in every European American and African American population tested (minimum $P = 1.74 \times 10^{-7}$ for the meta-analysis). This signal was GWS when individuals without cannabis exposure were excluded (minimum $P = 2.98 \times 10^{-8}$ for the meta-analysis).

Replication Results

The SNPs in Table 2 were tested for CAD association in the 2 replication samples (ICGHD and Yale-Penn 3). Table 3 shows the replication cohort-specific results for these SNPs, with the meta-analysis results from the discovery phase and the discovery + replication phase. The smallest *P* value in the ICGHD cohort among the 13 SNPs that could be reliably imputed and analyzed (this cohort was European Australian) was at rs74823926 ($P = .064$) in an intergenic region on chromosome 1. Several associations, however, were replicated in the Yale-Penn 3 sample (Table 3). The *P* values for 2 of the 3 GWS SNPs improved after meta-analysis with the replication cohorts (rs143244591 in *RP11-206M11.7*, from 1.38×10^{-8} to 4.32×10^{-10}; rs77378271 in *CSMD1*, from 2.84×10^{-8} to 2.13×10^{-8}), as did the *P* value for another SNP, rs146091982 in the solute carrier family 35 member G1 (*SLC35G1* [Ensembl ENSG00000176273]) (from 1.31×10^{-6} to 1.33×10^{-9}). The signal in *PI4K2B* also improved ($P = 5.57 \times 10^{-8}$ for the full meta-analysis). However, rs186825689 near *S100B* was no longer GWS ($P = 8.27 \times 10^{-8}$) in the full meta-analysis. The Figure shows Manhattan plots for the regions encompassing *RP11-206M11.7* (Figure, A), *SLC35G1* (Figure, B), *CSMD1* (Figure, C), and *PI4K2B* (Figure, D) in the discovery sample and after meta-analysis with the replication samples.

Cross-Disorder Analysis Results

The QQ plots of 5 Psychiatric Genomics Consortium traits (SCZ, bipolar affective disorder, autism spectrum disorder,

Table 3. Association Results in the Discovery and Replication Samples for the SNPs Shown in Table 2

SNP	*P* Value for Replication Cohort			*P* Value for Meta-analysis					
	Yale-Penn 3 Cohort[a]			Discovery Cohort[b]		Discovery + Replication Cohort[c]			
	African American	European American	ICGHD Cohort	African American	European American	African American	European American	All Participants	Direction[d]
rs74823926	9.40×10^{-3}	7.54×10^{-1}	6.36×10^{-2}	5.26×10^{-7}	6.36×10^{-1}	3.34×10^{-6}	1.59×10^{-1}	8.62×10^{-6}	+x+++-++
rs114383460	7.22×10^{-1}	NA	NA	1.09×10^{-6}	NA	1.93×10^{-6}	NA	1.93×10^{-6}	+x + xxx-xx
rs12621150	9.68×10^{-1}	1.15×10^{-1}	3.61×10^{-1}	7.67×10^{-1}	1.05×10^{-6}	7.75×10^{-1}	7.92×10^{-6}	5.13×10^{-4}	++++-+--+
rs7586604	2.80×10^{-1}	2.78×10^{-1}	6.04×10^{-1}	4.15×10^{-5}	6.19×10^{-3}	1.76×10^{-5}	1.69×10^{-2}	1.81×10^{-6}	-------+-
rs144605126	1.18×10^{-1}	NA	NA	8.67×10^{-7}	NA	3.84×10^{-6}	NA	3.84×10^{-6}	+x + x + x-xx
rs150064803	1.74×10^{-1}	NA	NA	3.41×10^{-7}	NA	1.41×10^{-6}	NA	1.41×10^{-6}	+x + x + x-xx
rs143020225	1.53×10^{-1}	NA	NA	7.19×10^{-7}	NA	1.95×10^{-7}	NA	1.95×10^{-7}	+x + xxx + xx
rs143244591	3.24×10^{-1}	NA	NA	2.18×10^{-8e}	NA	4.32×10^{-10e}	NA	4.32×10^{-10e}	+x + x + x+xx
rs73252553	6.40×10^{-1}	8.32×10^{-2}	4.10×10^{-1}	1.18×10^{-3}	2.28×10^{-5}	2.25×10^{-4}	5.45×10^{-6}	5.57×10^{-6}	++++++-++
rs28595532	8.06×10^{-1}	6.07×10^{-2}	2.24×10^{-1}	2.02×10^{-7}	1.08×10^{-1}	1.89×10^{-7}	1.52×10^{-1}	3.60×10^{-6}	+++++++++-
rs114311699	7.30×10^{-1}	NA	NA	3.78×10^{-7}	NA	2.75×10^{-7}	NA	2.75×10^{-7}	+x + x + x+xx
rs10066744	3.89×10^{-1}	NA	NA	4.82×10^{-7}	NA	2.27×10^{-7}	NA	2.27×10^{-7}	+x + xxx + xx
rs17665889	2.17×10^{-1}	1.17×10^{-1}	7.65×10^{-1}	1.51×10^{-1}	9.41×10^{-6}	2.69×10^{-1}	5.39×10^{-6}	8.41×10^{-4}	-+++-++-+
rs12534830	5.85×10^{-1}	8.67×10^{-1}	3.99×10^{-1}	7.76×10^{-1}	1.54×10^{-5}	1.05×10^{-2}	3.40×10^{-5}	1.12×10^{-6}	+++++++--+
rs77378271	9.25×10^{-2}	4.19×10^{-2f}	7.95×10^{-1}	2.13×10^{-1}	2.76×10^{-8e}	1.07×10^{-1}	5.16×10^{-8}	2.13×10^{-8e}	+-++x+++-
rs10969106	NA	5.50×10^{-1}	8.47×10^{-1}	NA	7.39×10^{-5}	NA	1.74×10^{-7}	1.74×10^{-7}	x + x + x+xx+
rs115553536	1.80×10^{-1}	NA	NA	6.46×10^{-7}	NA	2.14×10^{-6}	NA	2.14×10^{-6}	+x + x + x-xx
rs74400468	3.49×10^{-2}	6.61×10^{-1}	5.66×10^{-1}	5.53×10^{-2}	1.59×10^{-6}	1.22×10^{-2}	2.46×10^{-5}	9.82×10^{-7}	++-++++--
rs12218439	2.29×10^{-1}	1.01×10^{-1}	3.21×10^{-1}	1.01×10^{-6}	2.01×10^{-1}	4.91×10^{-6}	2.13×10^{-1}	4.20×10^{-4}	x++-++--+
rs146091982	8.84×10^{-4}	NA	NA	1.95×10^{-7}	NA	1.33×10^{-9e}	NA	1.33×10^{-9e}	+x + x + x+xx
rs73443003	2.53×10^{-1}	NA	NA	1.31×10^{-6}	NA	1.20×10^{-7}	NA	1.20×10^{-7}	-x-x-x-xx
rs200453611	7.29×10^{-1}	5.20×10^{-1}	9.40×10^{-1}	9.43×10^{-7}	6.24×10^{-1}	1.56×10^{-6}	5.34×10^{-1}	1.12×10^{-3}	+++++++++
rs200391037	9.28×10^{-1}	3.09×10^{-2f}	4.19×10^{-1}	1.02×10^{-1}	3.72×10^{-6}	1.04×10^{-1}	4.32×10^{-5}	1.10×10^{-5}	+++++++--+
rs193047854	6.74×10^{-1}	NA	NA	7.06×10^{-7}	NA	5.51×10^{-7}	NA	5.51×10^{-7}	+x + xxx + xx
rs199783889	4.38×10^{-1}	NA	NA	3.32×10^{-7}	NA	1.12×10^{-6}	NA	1.12×10^{-6}	+x + xxx-xx
rs78068107	2.90×10^{-2}	NA	NA	1.02×10^{-6}	NA	1.31×10^{-5}	NA	1.31×10^{-5}	+x + xxx-xx
rs186825689	4.51×10^{-1}	NA	NA	1.86×10^{-6}	NA	8.27×10^{-8}	NA	8.27×10^{-8}	+x + xxx-xx

Abbreviations: ICGHD, International Consortium on the Genetics of Heroin Dependence; NA, not applicable; SAGE, Study of Addiction: Genetics and Environment; SNP, single-nucleotide polymorphism.

[a] Indicates participants in the Yale-Penn cohort who did not undergo genotyping at the time of the discovery analyses.

[b] Indicates participants in the Yale-Penn cohort (Yale-Penn 1 and 2) who underwent genotyping for the discovery analysis and in the SAGE cohort.

[c] Indicates all cohorts.

[d] For the effect direction, the order of the symbols is the Yale-Penn 1 African American cohort, Yale-Penn 1 European American cohort, SAGE African American cohort, SAGE European American cohort, Yale-Penn 2 African American cohort, Yale-Penn 2 European American cohort, Yale-Penn 3 African American cohort, Yale-Penn 3 European American cohort, and the ICGHD European American cohort. + Indicates effect allele (listed in Table 2) is associated with an increase in cannabis dependence (CAD) criterion count, −, effect allele is associated with a decrease in CAD criterion count, and x, a valid effect estimate could not be obtained. See the Statistical Analysis subsection of the Methods section for an explanation of Yale-Penn 1, 2, and 3.

[e] Indicates genome-wide significant *P* values.

[f] Indicates $P < .05$ in the replication sample.

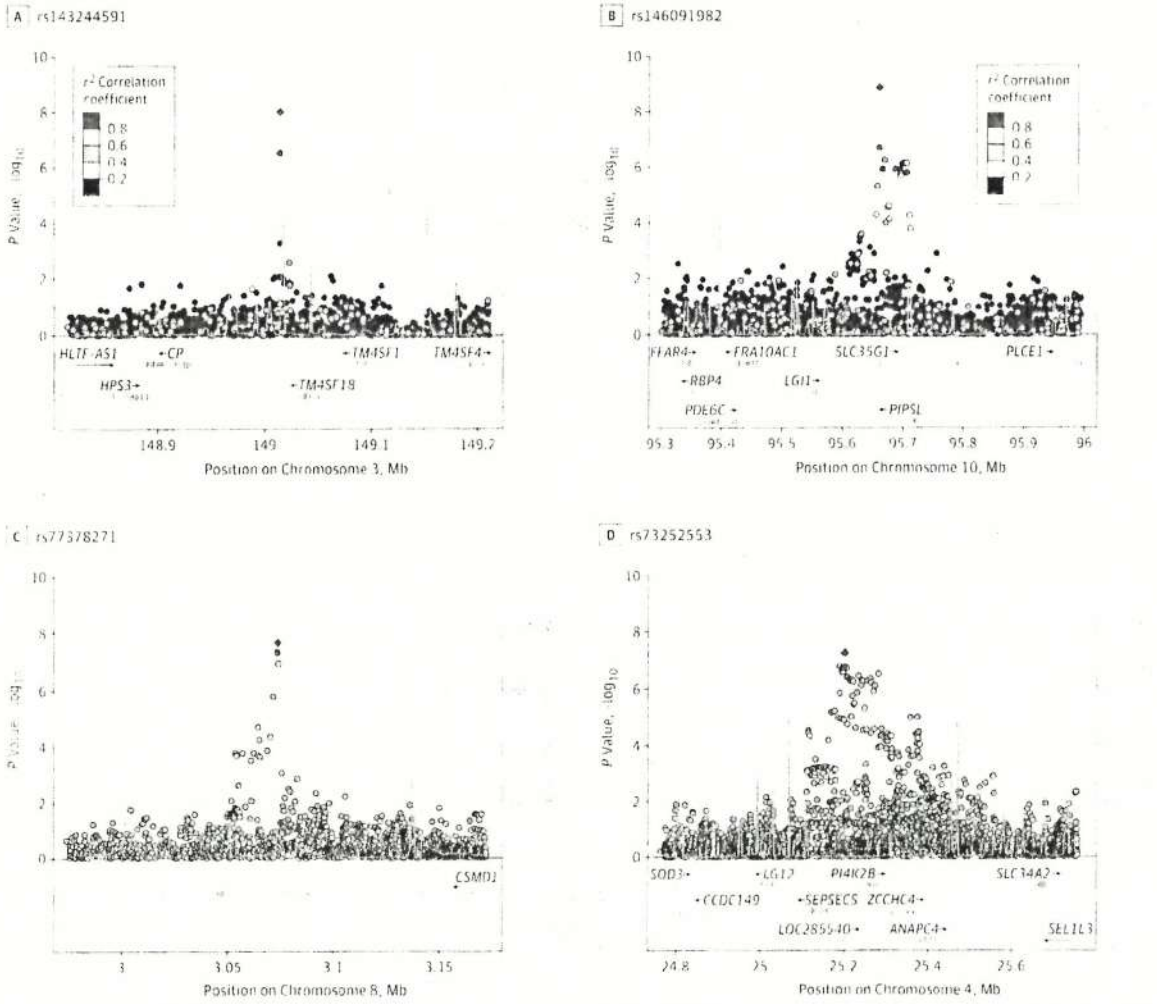
attention-deficit/hyperactivity disorder, and MDD) were stratified based on our CAD GWAS results at significance levels of $P < .05$, $P < .01$, $P < 1 \times 10^{-4}$, and $P < 1 \times 10^{-4}$. We observed enrichment of the MDD GWAS signal in the CAD GWAS (eFigure 4 in the Supplement) in European American participants, but no clear enrichment for the other 4 psychiatric disorders in either population group (eFigure 5 in the Supplement).

We used GPA to test the significance of pleiotropy between CAD and the same 5 psychiatric disorders (eMethods in the Supplement). For each disease pair, we estimated the percentage of SNPs shared by 2 diseases and tested the significance of pleiotropy (eTable 2 in the Supplement). The European American population yielded significant evidence of CAD-MDD pleiotropy ($P = 2.39 \times 10^{-6}$); genome wide, 1.7% of all imputed SNPs were estimated to be associated with both CAD and MDD. Of these, rs10954732 in P450 oxidoreductase (*POR* [OMIM 124015]) had the largest posterior probability (although not significant) of association with both traits ($P = 2.59 \times 10^{-6}$ for CAD; $P = .02$ for MDD; posterior probability, 0.70).

Discussion

We report herein the first GWS results for CAD to our knowledge. The sample includes a large proportion (18%-36%, depending on race and cohort) of individuals with CAD from 2 ancestral populations in 3 independent cohorts. We identified 3 regions with GWS SNPs imputed to the 1000 Genomes

Figure. Regional Manhattan Plots of Association Results for *DSM-IV* Cannabis Dependence Criterion Count in 4 Genomic Regions



Association results from single-nucleotide polymorphisms (SNPs) in 4 regions. A, The 148.8- to 149.2-MB region encompassing *RP11-206M11.7* on chromosome 3 in the Yale-Penn and Study of Addiction: Genetics and Environment (SAGE) African American participants. B, The 95.3- to 96-MB region encompassing *SLC35G1* on chromosome 10 in the Yale-Penn and SAGE African American participants. C, The 2.8- to 4.8-MB region on chromosome 8 encompassing *CSMD1* in the Yale-Penn, SAGE, and International Consortium on the Genetics of Heroin Dependence (ICGHD) African American and European American participants. D, The 25.07- to 25.43-MB region encompassing *PI4K2B* on chromosome 4 in the Yale-Penn, SAGE, and ICGHD African American and European American participants. In A and B, the SNPs are color coded according to the correlation coefficient (r^2) in the 1000 Genomes African samples with the most significant SNP. In C and D, results from the African American and European American participants were combined, and no linkage disequilibrium information was displayed. The light purple circle represents the $-\log_{10}$ *P* value for the most significant regional SNP in the meta-analysis of the discovery samples, the purple diamond, the result for that SNP after meta-analysis with the replication sample(s). The light blue line and right y-axis show the observed recombination rate.

reference panel that implicate several biological processes and provide insight into the biology of CAD, including evidence of an inflammatory component in the disorder, which may also mediate risk for SCZ[36] and MDD.[37,38] The smallest *P* value observed ($P = 4.32 \times 10^{-10}$) was at rs143244591 in *RP11-206M11.7*. Little is known about this antisense transcript or which, if any, genes it regulates. Minor alleles were protective. The next most significant locus was *SLC35G1* (rs146091982, $P = 1.33 \times 10^{-9}$), a potential member of the drug/metabolite transporter superfamily (EamA, previously DUF6). Ubiquitously expressed, *SLC35G1* binds stromal interaction molecule 1, a calcium sensor that communicates the calcium load within the endoplasmic reticulum to store-operated channels in the plasma membrane[39] when calcium stores in the endoplasmic reticulum are depleted.[40] The *SLC35G1*-stromal interaction molecule 1 complex likely regulates the activity of the transporters that coordinate cytosolic calcium through modulation of pump activities.[40] The third GWS locus, *CSMD1* (rs77378271; $P = 2.13 \times 10^{-8}$), is highly expressed in the growth cones of developing central nervous system neurons, where it likely acts as a regulator of complement activation and inflammation.[41] Different SNPs in *CSMD1* have been associated with SCZ at the GWS level.[42] Thus, *CSMD1* is the second

gene to be implicated in both disorders (after *NRG1*[16]) and may explain at least part of their shared genetic susceptibility.

Two other established SCZ risk genes, *RIMS1* (OMIM 606629) (minimum SNP, $P = 1.59 \times 10^{-5}$) and *MEF2C* (minimum SNP, $P = 5.22 \times 10^{-5}$), showed suggestive association with CAD. *MEF2C* is highly expressed in developing mammalian neurons and is thought to mediate calcium-dependent survival of neurons that have made the appropriate synaptic connections.[43] From a biological perspective, *RIMS1* is immediately relevant; RIMS1 acts as a scaffold protein that regulates synaptic vesicle exocytosis, affecting cannabinoid receptor 1 (*CB1*)-mediated long-term suppression of γ-aminobutyric acid release, ultimately mediating presynaptic forms of long-term plasticity.[44] Minor alleles at rs142307709 in *RIMS1* were associated with fewer CAD criteria in African American participants. We observed at least a nominally significant signal in both Yale-Penn African American analysis subsets and a nonsignificant trend in SAGE African American participants.

Limitations of the GWAS findings should be noted. One of the significant SNPs identified (rs1432147591 on chromosome 3) has little supportive evidence for association from other SNPs in the region, possibly owing to low linkage disequilibrium. However, despite stringent imputation quality thresholds for including SNPs in the analysis ($r^2 \geq 0.8$) and evidence of an association in the replication sample, this signal may represent an imputation artifact. Second, although none of the GWS SNPs identified in the full GWAS analysis are rare, they could be described as infrequent, with minor allele frequencies in a range sometimes associated with false-positive results (4%-6%). Also, of the GWS regions, only *CSMD1* showed evidence of associations in European American and African American participants. The region containing *PI4K2B*, which became GWS after excluding unexposed individuals (see below), was also at least nominally associated with CAD in both populations. The 2 African American–specific SNPs were rare or monomorphic in European American participants. The lack of association in European American participants could be owing to different linkage disequilibrium patterns or the absence of causal variants. The Yale-Penn samples who underwent genotyping on the HumanOmni1-Quad and Human Core Exome chips showed more consistent results than the corresponding SAGE population, which is not surprising insofar as SAGE participants were recruited from different areas and ascertained using different criteria (AD, CD, and OD in Yale-Penn and primarily AD and ND in SAGE). The difference in ascertainment criteria (use of licit vs illicit drugs) across studies likely explains the fact that the proportion of cannabis-exposed individuals varied significantly across cohorts (2293 in SAGE population [76.9%] and 7626 in the Yale-Penn population [85.0%]). The limitations of phenotypic distribution and population differences are more relevant to the Australian ICGHD replication cohort and may explain the lack of replication in this cohort. Despite this, we obtained statistically significant evidence for formal replication for the SNP in *SLC35G1* and stronger evidence for association at many of the top SNPs after including the replication samples. Finally, these cohorts have higher rates of polysubstance dependence than the general population and may not be generalizable to individuals who only use cannabis.

Effect of Exposure Strata and Comorbidity

Because the inclusion of genetically at-risk individuals who never initiated cannabis use might have influenced our results, we repeated the primary analyses in the discovery cohort after removing unexposed individuals. Two of the 3 regions identified remained GWS (eTable 1 in the Supplement). The *P* value for rs1432147591 on chromosome 3 improved slightly ($P = 1.13 \times 10^{-8}$, meta-analysis exposed) and was associated at $P \leq .02$ in each of the African American subgroups. The signal at rs77378271 in *CSMD1* was almost identical ($P = 2.95 \times 10^{-8}$, meta-analysis exposed) and showed association at $P < 5.07 \times 10^{-4}$ in 2 of the 3 European American subgroup and at $P = 4.46 \times 10^{-3}$ in 1 of the African American subgroups. In addition, the block of SNPs in and around *PI4K2B* became GWS with a consistent effect direction (minor alleles being protective) in every European American and African American population tested and became GWS (minimum $P = 2.98 \times 10^{-8}$, meta-analysis exposed, at rs147170184). The evidence for pleiotropy between CAD and MDD was attenuated substantially ($P = .60$) after excluding unexposed participants. That the removal of unexposed individuals from the analysis had a relatively minor effect on the primary findings and actually improved the strength of some suggests that any loss in power owing to the smaller sample was offset by an increase in phenotypic precision. In the pleiotropy analysis, which relies on genome-level association results and is not limited to the most significantly associated SNPs, the power loss apparently outweighed any increase in precision. The significance of each of the top SNPs was modestly attenuated after adjusting for the *DSM-IV* criterion counts for AD, CD, and OD (eTable 1 in the Supplement).

Ion Homeostasis and Addiction

The previously published GWAS of OD[19] and CD[20] in a subset of this sample each identified risk genes and pathways involved in the regulation of neuronal calcium and potassium, and the pathway involving synaptic long-term potentiation was also identified for OD. Also, a cross-disorder analysis identified calcium signaling in neurons as a pathway mediating 5 psychiatric diseases, including SCZ and MDD.[45] The GWS association in *SLC35G1* and GWS (in the discovery sample only) associations in and around *S100B* suggest ion homeostasis may play a role in CAD risk.

Shared Risk for CAD and Other Psychiatric Disorders

Many previous studies[7,8,45,46] have focused on the relationship between CAD and SCZ, whereas the correlation between CAD and MDD has received much less attention. Although depressive disorders are highly comorbid with CAD in clinical settings,[47] to our knowledge no previous genomics study has explored CAD-MDD pleiotropy. We found some evidence for genetic correlation between the risks for CAD and MDD. The existence of shared genetic factors for CAD-MDD is supported by the overlap in SNPs nominally associated with both traits, although we found no significant evidence of pleiotropy at any single SNP. We also found limited support for the possibility that such a relationship exists for CAD and SCZ based on relatively strong signals for both traits with variants in *CSMD1* (although not the same variants). Nongenetic explanations such as

patients with SCZ or MDD mediating the symptoms of these disorders with cannabis use might also explain the comorbidity. These analyses are exploratory, and follow-up studies to validate and extend these findings are necessary.

Conclusions

This study provided the first GWS evidence to our knowledge for SNPs associated with CAD via GWAS in 3 distinct genomic locations. These findings will lead our understanding of genetic vulnerability to CAD in new directions that can inform our understanding of the biology of CAD. We obtained entirely novel evidence of genetic overlap between CAD and MDD and conclude that *CSMD1* may be a candidate gene that affects the risk for CAD and SCZ, a topic of considerable research interest. These results also suggest that common pathways (nervous system development, inflammation, and ion homeostasis) mediate the risk for multiple psychiatric disorders and dependence on multiple substances, including cannabis.

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