FALL 2013

UPMC SYNERGIES

Cannabis Revisited

ANTOINE DOUAIHY, MD
Associate Professor of Psychiatry
University of Pittsburgh School of Medicine
Medical Director of Addiction Medicine Services
Western Psychiatric Institute and Clinic of UPMC

This publication describes the major characteristics unique to cannabis, both to the drug itself and to the societal context of its use, including an overview of the epidemiology of cannabis use and a discussion of cannabis and the brain. The article also reviews current research related to the medical and neuropsychological effects associated with cannabis consumption, prevention and treatment approaches targeting cannabis-related problems, and cannabis control policy. This review concludes with recommendations and strategies pertaining to cannabis use.

Unique Dilemmas Associated With Cannabis

Cannabis, produced from the *Cannabis sativa* plant, is used in three forms: herbal cannabis, the dried leaves and flowering tops, also known as "cannabis" or "weed," among others; cannabis oil, a mixture resulting from extraction of active ingredients of the plant; and cannabis resin, the pressed secretions of the plant, known as "hashish." Herbal cannabis is the most frequently used form of cannabis in much of the world.

The greatest challenge faced when discussing cannabis and its use is misguided information, or little information. For the past few decades, cannabis control policy has been the focus of an ongoing debate in the United States and other countries. Those advocating policy reform claim there is no proof that prohibition reduces drug use,[1] and those promoting continued prohibition[2] have attempted to support their position with specific and sometimes inaccurate claims regarding the risks and consequences. As a result, they have created confusion among recreational and medical users of cannabis, as well as a little-informed or misinformed general public with no clear knowledge of what risk and harm is associated with cannabis use.

Accreditation Statement

The University of Pittsburgh School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The University of Pittsburgh School of Medicine designates this enduring activity for a maximum of **0.5 AMA PRA Category 1 Credits™**. Each physician should only claim credit commensurate with the extent of their participation in the activity. Other health care professionals are awarded (0.05) continuing education units (CEU), which are equivalent to 0.5 contact hours.

Disclosures

Dr. Douaihy has no relationships with proprietary entities producing health care goods or services.

Instructions

To take the CME evaluation and receive credit, please visit **UPMCPhysicianResources.com/Psychiatry** and click on the course *UPMC Synergies* Fall 2013.

ADDRESS CORRESPONDENCE TO:
Western Psychiatric Institute and Clinic of UPMC
3811 O'Hara St.
Pittsburgh, PA 15213
1-877-624-4100

Second, it is important to distinguish between the whole cannabis plant material and some individual components within the cannabis plant. Some constituents of cannabis, including Delta 9 Tetrahydrocannabinol (THC) are available today in pill form, dronabinol or Marinol®; some synthethic mimetics of those constituents are also available, nabilone or Cesamet®. On the other hand, the cannabis plant has thousands of unknown and carcinogenic components that have not been accepted by the scientific community as medicines. An exhaustive review by the U.S. Institute of Medicine concluded that smoked cannabis should "generally not be recommended for medical use."[3] In addition, smoked cannabis has a wide variation of effective dose, due to individual differences in absorption and metabolism, as well as depth of inhalation and retention of inhaled smoke.[4] Medical cannabis laws in some states bypassed barriers to the drug's medical use by its Schedule I classification under the 1970 Controlled Substances Act, therefore allowing patients to obtain cannabis with a written prescription from a physician. The cannabis that patients obtain will not have been subjected to standardization of the active ingredients and routes of administration, nor to the overall quality control procedures of conventional pharmaceuticals. This could create more challenges to the circumstances in which harm reduction is approached and implemented.

Finally, there is no one profile of a cannabis user. As Erich Goode discussed in the book *Drugs in American Society*,[5] individuals using cannabis are on a continuum profile of use consequences. It is important to assess the user's profile (circumstances and consequences of use) in order to identify the appropriate approach.

Jim and Janie, both 35, are happily married, ambitious, and successful professionals with two young children. They are also cannabis smokers. They light up only on weekends, only at night, and only when the kids are asleep. Cannabis plays a recreational and fairly minor role in their lives, much as going to the movies and drinking wine with dinner do. There are many weeks when they don't indulge, and when they do, they share just one joint.

Tim, 15, is a high school student doing so poorly academically that he is on the verge of dropping out. This year, he missed nearly half of his classes, and he snoozes through many of those he does attend. He lights up a joint as soon as he is awake, and he smokes four or five more joints during the day and just before he goes to bed. Tim is high just about all his waking hours: he is obsessed with weed.

Epidemiology of Cannabis Use

Cannabis use is the highest among illicit drugs globally. In many countries, cannabis use increased in the early 2000s; however, its use recently started stabilizing or slightly decreasing. Rates of use are not low. In 2009, it was estimated that between 125 and 230 million people — between 2.8% and 4.5% of the world population aged 15 and 64 — used cannabis at least once during the past year. Though use in North America has remained relatively stable, use in the United States has increased slightly over the past four years. Annual prevalence of cannabis use in North America is approximately 10.7% of the population aged 15-64, and youth use has risen over the past four years.[6] Current use rates are highest in the young adult years (i.e., 18-25; 16%) relative to younger (10%) or older (4%) age groups.

Cannabis and the Brain

The active ingredient in cannabis, THC, is only found in small parts of the cannabis plant. THC stimulates the cannabinoid receptors (CB1, CB2, and others) located on the surface of neurons to produce psychoactive effects. CB receptors are components of the endocannabinoid system in the brain that plays a role in neural development and function. CB receptors are typically activated by a naturally occurring neurotransmitter, anandamide. The CB2 receptor does not trigger psychoactive effects. THC mimics anandamide, binding well with the CB1 and CB2 receptors and activating the neurons. However, the effects of THC are more potent and longer-acting than the endogenous neurotransmitter. CB receptors are widely present in the brain, but are particularly prevalent in certain brain regions, such as the cerebellum, hippocampus, amygdala, and prefrontal cortex — brain regions involved in pleasure, reward, cognition, memory, motor coordination, and pain perception.[7] Activating CB receptors regulates the release of multiple neurotransmitters, including GABA, serotonin, dopamine, and noradrenaline.[8]

While THC is the main psychoactive component in cannabis extracts, cannabis contains at least 489 chemical compounds, 70 of which are cannabinoids. Two main components, cannabinol and cannabichromene, have slight THC-like effects. Furthermore, cannabis contains some quantities of cannabinoid carboxylic acids, which lack psychoactive effects until they are heated during smoking, which turns them into an active form of THC. [9]

Cannabis is typically smoked in a water pipe or joint, because that is the fastest way for the drug to reach the brain and produce the psychoactive effects. THC passes from the lungs into the bloodstream, and reaches the brain, producing the effects almost instantly. Smoked cannabis produces a high that lasts from one to four hours, and delivers more THC into the bloodstream than eating or drinking the drug. Acute effects of use are usually temporary and reversible, and do not present a risk of harm. A few minutes after using, heart rate increases, the bronchial system relaxes and becomes enlarged, and the eyes become red as the blood vessels expand. Users typically report feelings of euphoria and relaxation. As those effects taper down, some users experience sleepiness, while others may feel anxious or paranoid. Even a small percentage of users could experience psychotic manifestations, depending on genetic and vulnerability characteristics (more details later in the review).[10]

Synthetic cannabinoids, also known as “K2” or “Spice,” are emerging as a new drug of abuse. These substances are a combination of herbs and spices that are mixed with synthetic compounds chemically similar to THC. Synthetic cannabinoids are often purchased in tobacco shops or over the Internet, and typically smoked. The effects of these substances are similar to those of cannabis. The lack of standardization of synthetic ingredients makes them dangerous since users are not aware of exactly what products they are inhaling.[11]

Medical and Neuropsychological Effects of Cannabis Misuse

In the following section, we summarize the most relevant findings related to the consequences of cannabis misuse. These findings reflect varying levels of empirical support and are subject to change as new studies continue to emerge.

Cannabis, Personal Development, Learning, and Life Outcomes

There is mounting evidence demonstrating a strong relationship between frequent cannabis use and poorer educational and social outcomes in adolescents and young adults. A recent study found that cannabis use is linked with dropping out of school, and subsequent unemployment, social welfare dependence, and an overall feeling of inferior life satisfaction compared to noncannabis teen users. These results remained significant even after controlling for family socio-economic background, family functioning, exposure to child abuse, early adolescent academic achievement, and comorbid psychiatric and substance use disorders.[12] A comprehensive meta-analysis examining four dozen studies by Mcleod and colleagues showed that cannabis use is consistently associated with reduced grades and a reduced chance of graduating from school.[13] This is consistent with the U.S. National Survey on Drug Use and Health, which found that youth with poor academic results were more than four times likely to have used cannabis in the past year than youth with an average of higher grades. In a related survey of 6,000 students age 13 to 23 conducted by the RAND Corporation, teens who smoked cannabis from once a week to monthly at age 13, decreased their abuse by age 18, and as young adults smoked three to 10 times a year, lagged behind all other groups in education and earnings when surveyed at age 29.[14]

Furthermore, the National Institute on Drug Abuse (NIDA) has identified many studies associating employee cannabis use with negative outcomes, such as increased absences, accidents, workers' compensation claims, and job turnover.[15] The impact of cannabis use on interpersonal relationships was demonstrated in a study that showed that high levels of cannabis use were associated with lower satisfaction with intimate romantic relationships and lower satisfaction with life, including both work and leisure pursuits.[12]

The causal effect of frequent and chronic cannabis use on educational, occupational, and interpersonal outcomes is not clear. However, it could be attributed to the negative effects on cognition, even after the short-term consequences of the drug recede.[16]

Cannabis and Cognition

Adolescents who use cannabis are at risk for a number of harmful drug-related consequences. Acute cognitive impairment from using cannabis may include difficulties with concentration, prolonged reaction time, short-term memory deficits, increased errors in simple visual or auditory tasks, and poor fine motor control and coordination. These changes are most likely related to a decrease in attention.[17] There are contradictory findings concerning whether cognitive impairment persists once cannabis use has stopped.[18,19] However, in a laboratory setting, cannabis and THC produce dose-related deficits in reaction time, attention, motor performance and coordination, and information processing that can last up to 28 days after abstinence from the drugs.[10] There is generally good agreement between the conclusions based on evidence-based effects of cannabis on cognitive functions and the clinical impression based on population studies.[10] Beginning use at an early age may influence the long-term effects on cognition.[20] In addition, teens who continue to use cannabis heavily show poorer complex attention functioning, as well as poorer sequencing ability, slower psychomotor speed, and difficulties in verbal story memory.[16]

Functional imaging studies have found lower activity levels in regions of the brain involved in memory and attention, such as the hippocampus and prefrontal cortex, in chronic cannabis users. Heavy chronic users may have reduced volumes of the hippocampus and amygdala.[10] The significance of these findings is clear. Relatedly, there is no evidence of significant structural damage to the brain from cannabis use.[21,22]

Recent reports indicated that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at earlier ages, and more adolescents are using cannabis on a daily basis. A recent study showed that persistent cannabis use was associated with neuropsychological decline broadly across domains of function, even after controlling for years of education. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Additionally, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users.[23] These findings indicate the neurotoxic effects of cannabis on the adolescent brain and highlight the importance of implementing prevention and policy changes targeting cannabis use in adolescents.

The problem of cannabis use and driving has been documented in numerous studies. Cannabis use may increase the risk of road accidents in drivers under the influence due to the impairment of motor coordination and reaction time.[24] A major nationally representative U.S. sample found that more than 8% of weekend, nighttime drivers tested positive for cannabis, nearly four times the percentage of drivers at the U.S. legal limit for alcohol while driving (e.g., Blood Alcohol Content, BAC of 0.08 or more).[25] Additionally, another study showed that there were 126 fatalities in single-car crashes with cannabis-involved drivers, three-quarters of whom had BAC levels below the legal limit of 0.08.[26] The strongest evidence for linking cannabis use and driving comes from a meta-analysis of nine studies. The analysis found that cannabis use was linked to heightened risk of crash involvement, even after controlling for different variables.[27] This study also reported that the risk of crash involvement increased along with an increase in frequency in cannabis potency (tested through urine drug testing) and self-reported frequency of use. Though research has clearly demonstrated the connection between cannabis use and impaired driving, this issue remains a major policy challenge.[24]

Cannabis and Psychiatric Disorders

Earlier studies showed that early-onset cannabis use (before the age of 15) and frequent use (at age 21) may increase the risk of depression in young adulthood.[28] However, more recently, there was no evidence for an increased risk of depression among those who used cannabis by age 18 to 20.[29] The association between cannabis use and subsequent severe depression was likely to be confounded by common risk factors for both, such as disturbed behavior during childhood.[29]

There is a strong pattern of cannabis relieving anxiety at low doses and promoting anxiety at higher doses.[30] Daily cannabis use was associated with anxiety disorder at age 29 years, as was cannabis dependence. Among weekly adolescent cannabis users, those who continued to use cannabis at 29 years remained at significantly increased odds of anxiety disorder.[31]

There is significant evidence that cannabis use in individuals vulnerable to schizophrenia enhances the risk of an acute episode.[32] Furthermore, patients with psychosis who continue to abuse cannabis are more likely to have frequent hospitalizations, poorer psychosocial outcomes, and earlier relapse to psychosis compared to those who do not continue use.[33] Finally, there is robust evidence for a relationship between cannabis use and earlier onset of psychotic illness.[34] This meta-analysis supported the hypothesis that cannabis use plays a causal role in the development of psychosis in some patients, depending on their genetic makeup, age at first use, and other factors. Of course, causality is challenging to establish since many cannabis users use other drugs.[35] The results reemphasize the importance of addressing the potentially harmful effects of cannabis use.

Cannabis and Addiction

Long-term use of cannabis can lead to tolerance to the effects of THC and dependence. It is estimated that 9% of those who have used cannabis at least once met the criteria for cannabis dependence at some point in time.[36] Among people who use cannabis heavily, the percentage meeting those criteria may be as high as 50%.[37] Those who begin using the drug in their teens have a one in six or seven risk of cannabis dependence.[38] Higher potency of cannabis may contribute to an increase of the number of cannabis users becoming dependent.[39] Those who initiate use earlier are at higher risk of developing dependence.[38,40] Additionally, more than two-thirds of treatment admissions involving those under the age of 18 report cannabis as their primary substance of abuse, more than three times the rate for alcohol and more than twice for all other drugs combined. This data (1992-2006) also showed that the rates of admissions for children and teens under age 18 for cannabis as the primary substance of abuse increased by 188% while other drugs remained steady.[40]

The impact of cannabis dependence is mostly seen in abusers who reach out for treatment to quit using. The individuals seeking treatment are mostly motivated by negative psychosocial consequences, interpersonal difficulties, loss of self-control, and diminished productivity.[41,42]

A cannabis withdrawal syndrome has been identified and characterized by irritability, anger, anxiety, insomnia, dysphoria, craving, and appetite disturbance. The onset of withdrawal is within 24 to 48 hours of abstinence, and peak effects occur between four to eight hours. This syndrome usually lasts from one to three weeks and has been estimated to be comparable in severity to nicotine.[43]

The "gateway" effect of cannabis has been debated over many years. Recently, a study evaluated the influence of cannabis use patterns on the probability of initiation with other illicit drugs. In this retrospective cohort on drug use, modeling was done of all possible pathways from initial abstinence to cannabis initiation, daily cannabis use, and other illicit drug initiation. The model was adjusted for tobacco and alcohol use. The results of the study revealed that the risk for illicit drug initiation appeared 21 times higher among cannabis experimenters and 124 times higher among daily cannabis users than among nonusers. These results provide strong support for a stage process of drug use mediated by cannabis and liable to lead to other illicit drug experimentation, and are compatible with the gateway theory.[44]

Cannabis and Pregnancy

Cannabis use during pregnancy may cause harm to the fetus. Subtle disturbances of cerebral development resulting in cognitive impairment in the offspring of women who used cannabis during pregnancy have been reported.[45,46] However, associations that have been reported are subject to confounding variables, mostly because cannabis users are more likely to use other drugs, tobacco, or alcohol during pregnancy.

Cannabis and Respiratory and Cardiovascular Systems

Cannabis smoke is composed of many of the same ingredients that exist in tobacco smoke (e.g., carbon monoxide, cyanide), with the exception of THC in cannabis and nicotine in tobacco. Heavy cannabis smokers have a higher risk than nonsmokers of bronchial and lung clinical manifestations, such as daily cough, chronic bronchitis, and lung infections and pneumonias.[47,48] There is a four-fold greater quantity of cannabis smoke particles in the respiratory tract than generated from the same amount of smoked tobacco. This is attributed to differences in the way cannabis is smoked compared to tobacco. For example, cannabis smokers have a tendency to hold their breath significantly longer than tobacco smokers.[48] In addition, bronchial biopsies of cannabis smokers have detected signs of airway inflammation similar to the changes seen in tobacco smokers, and provide some evidence of precancerous change suggestive of higher risk of respiratory tract cancers.[49,50]

Cannabis and THC cause a dose-dependent increase in heart rate, raising concerns in patients with cardiovascular disease. Cannabis use can contribute to a 4.8-fold increase in the risk of myocardial infarction in the hour after use, and provokes angina in patients with underlying cardiovascular disease.[51,10]

Cannabis and Cancers

Accumulating evidence suggests that smoked cannabis is associated with or a causative agent in specific cancers. On the other hand, preclinical research revealed that cannabinoids in not-smoked cannabis may play a potential role in the treatment of various cancers.[52]

Prevention and Treatment of Cannabis Use Disorders

Cannabis prevention efforts are crucial because cannabis is often the first illicit drug used by youth. It is clearly established that prevention is cost-effective. A comprehensive, multisector, communitywide approach to cannabis prevention incorporates evidence-based processes that include: assessing prevention needs based on epidemiological data; building community prevention capacity; developing a strategic plan; implementing effective community prevention policies and practices; and evaluating outcomes of the plan. This approach involves the community on multiple levels: individuals, families, schools, workplaces, and the community at large. An example of this approach has been evaluated in many countries, including the United States. In 2010, an independent evaluation showed that communities with such coalitions had positive outcomes, meaning significant reductions in alcohol, tobacco, and cannabis use among middle and high school-age youth, while perception of risk increased.[53] Other interventions also have demonstrated effectiveness, such as family-based approaches and life-skills building.[54]

Treatment for cannabis use disorders has included three modalities: cognitive-behavioral therapy (CBT), motivational enhancement therapy (MET), and motivational incentives or contingency management (CM). To date, there are 11 systematic studies of treatments for adult cannabis users.[55,56] CBT's central element is anticipating triggers for use and helping patients develop effective coping strategies. MET is an adaptation of Motivational Interviewing[57] and focuses on helping users resolve their ambivalence about making changes and strengthening their motivation for quitting by evoking change talk and commitment language. CM involves rewarding patients for achieving abstinence, verified by drug-free urine samples, using monetary or other incentives. Combining the three modalities appears to produce the best outcomes in terms of achieving abstinence. Abstinence rates are roughly 25% one year after treatment. These results point to the importance of understanding cannabis dependence as a chronic illness requiring long-term treatment.

CBT and MET approaches have been evaluated and adapted for adolescent cannabis abusers and compared to family therapy and community reinforcement modality in a large multisite study.[58] These modalities seem to lead to significant but modest reduction in cannabis users. One explanation to these results is the fact that adolescents usually are indirectly or directly pressured into treatment.

To date, no medication has proved to work for cannabis dependence. However, various medications are under investigation to harness the new knowledge and therapeutic potential of the cannabinoid system.[7]

Cannabis Control and Policy Measures

The United States outlawed cannabis on a federal level in 1973, with the passage of the Marijuana Tax Act. However, today several states have formal decriminalization laws. This debate is highly controversial because even in jurisdictions without a formal decriminalization law, people are rarely jailed for possessing small amounts of cannabis. In fact, the rate of arrest for each "joint," or cannabis cigarette, smoked is about one arrest for every 12,000 joints.[59] This probably explains why the information on early decriminalization effects on use has been mixed. This also probably explains why some studies found a positive relationship between greater use and formal changes in the law.[60]

Recent reports from the RAND Corporation concluded that legalization would result in lower cannabis prices and thus increases in use (though by how much is uncertain), and that legalizing cannabis in California would not dramatically reduce the drug revenues collected by Mexican drug trafficking organizations from sales to the United States.[59]

Recently, Hall[61] summarized the costs potentially associated with enforcing cannabis prohibition, which are the basis for arguments favoring liberalizing cannabis control policies, and concluded that there are many unknowns about the consequences of a more liberal cannabis use policy.

Over the past two decades, the concept of cannabis as medicine has become increasingly popular. Beginning in 1996, states started to vote by referenda to allow the use of "medical" cannabis. Some components of cannabis have been reported as helpful for some medical conditions, such as glaucoma, multiple sclerosis, pain, and nausea, though the evidence is scarce when compared to sample size, length of

studies, and lack of standardization of the active ingredients required for new drug approval.

People taking scientifically approved cannabis-based medications are different from people who seek to use medical cannabis as a cover for legitimizing overall cannabis use. According to a 2011 study that examined 1,655 applicants in California who sought a physician's recommendation for medical cannabis, very few of those who sought a recommendation had cancer, HIV/AIDS, glaucoma, or multiple sclerosis.[62] The use of cannabis under the shield of medicine also has affected youth drug use patterns. A recent study looked at two separate sets of data and found that residents of states with medical cannabis had cannabis abuse/dependence rates almost twice as high as states without such laws.[63] Another study found that among youths age 12 to 17, cannabis use rates were higher in states with medical cannabis laws (8.6%) than in states without such laws (6.9%).[64] More research is needed to elucidate this link.

Conclusion

Recent data on cannabis use clearly shows that it is associated with harm to the individual and to society. Negative consequences occur, particularly in chronic and heavy users. The increased cannabis-related emergency department visits and admissions and the rise in potency of cannabis from 3% to 10% from 1990 through 2008, illustrate the danger of today's highly potent cannabis and its potential to threaten both public health and public safety.[6] Cannabis use is linked to addiction, cognitive impairment, motor skills deficits, respiratory and cardiovascular problems, and an increased risk of psychosis. Cognitive impairment may persist in heavy users after discontinuation of use. Chronic cannabis use by adolescents may interfere with educational attainment and other adult psychosocial outcomes.

Comprehensive, accurate information, and harm-reduction strategies concerning cannabis should be disseminated to those who are using cannabis or are thinking about doing so. Individuals who are using cannabis for medical purposes without the benefit of pharmaceutical industry quality controls need to be informed about potential risks associated with cannabis use, particularly in vulnerable populations: those with cardiovascular and respiratory disease, pregnant women, and individuals with predisposition to psychosis. Cannabis use by children and young adolescents should be strongly discouraged due to the potential damage to maturing brains and the increased risks of serious adverse outcomes, as discussed above. There are several evidence-based prevention and treatment strategies that can be implemented to prevent use, and effectively treat cannabis use disorders and reduce negative consequences.

Criminal penalties for cannabis possession by adults should be eliminated. Legislation that decriminalizes cannabis use is needed. However, outright legalization of cannabis use based primarily on arguments for civil liberties and low harm potential is not recommended because real and serious harms do occur, and the effect of legalization is highly unpredictable. Research at both individual and societal levels is needed to better understand the consequences of cannabis use and the effects of various types of policy change on rates of problematic cannabis use.

References

1. Zimmer L, Morgan JP. Marijuana myths, marijuana facts: A review of the scientific evidence. New York: *Lindesmith Center,* 1997.
2. Drug Enforcement Administration. The DEA position on marijuana. Retrieved January 1, 2008, from *www.usdoj.gov/deal/marijuana_position.html.*
3. Joy JE, Watson SJ, & Benson JE (Eds). Marijuana and medicine: assessing the science base. Washington, DC: *National Academy Press,* 1999.
4. Gorelick DA & Heisman SJ. Methods for clinical research involving cannabis administration. In Methods in Molecular Medicine: Marijuana and Cannabinoid Research: Methods and Protocols (Ed. E.S. Onaivi). New Jersey: *Humana,* 2006.
5. Goode E. Drugs in American Society (7th ed.). New York: McGraw-Hill, 2008.
6. SAMSHA, National Household Survey on Drug Use and Health, 2011; NIDA, Monitoring the Future, Dec. 2010.
7. National Institute on Drug Abuse. Research Reports Series: Cannabis Abuse, 2010.
8. Moreira FA & Lutz B. The endocannabionoid system: Emotion, learning, and addiction. *Addiction Biology* 2008;13:196-212.
9. Maldonado R, Berrendero F, et al. Neurochemical basis of cannabis addiction. *Neuroscience* 2011;181:1-17.
10. Hall W & Degenhardt L. Adverse health effects of non-medical use of cannabis. *Lancet* 2009;374:1383-1391.
11. United States Drug Enforcement Administration, Drug Fact Sheet: K2 or Spice, 2011.
12. Ferguson DM & Boden JM. Cannabis use and later life outcomes. *Addiction* 2008;103:969-976.
13. Macleod J, Oakes R, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 2004;363:1579-88.
14. Ellickson PL, Martino SC, & Collins RL. Cannabis use from adolescence to young adulthood: multiple developmental trajectories and their associated outcomes. *Health Psychology* 2004;23(3):299-307.
15. National Institute on Drug Abuse. Research Report Series; Cannabis Abuse. Accessed November 2011 at *http://www.drugabuse.gov/ResearchReports/Cannabis/cannabis4.html.*
16. Schweinsburg AD, Brown SA, & Tapert SF. The influence of cannabis on neurocognitive functioning in adolescents. *Curr Drug Abuse Rev* 2008;1(1):99-111.
17. Leweke FM, Kampmann C, et al. The effects of tetrahydrocannibol on the recognition of emotionally charged words; an analysis using event-related brain potentials. *Neuropsycholobiology* 1998;37:104-111.
18. Bolla KI, Brown K, et al. Dose-related neurocognitive effects of marijuana use. *Neurology* 2002;59:1337-1343.
19. Bolla KI, Eldreth DA, et al. Neural substrates of faulty decision-making in abstinent marijuana users. *NeuroImage* 2005;26:480-492.
20. Pope HG, Gruber AJ, et al. Early onset cannabis use and cognitive deficits: What is the nature of the association? *Drug and Alcohol Dependence* 2003;69(3):303-310.
21. DeLisi LE, Bertisch HC, et al. A preliminary DTI study showing no brain structural change associated with adolescent cannabis use. *Harm Reduction Journal* 2006;3:17-22.
22. Tzilos GK, Cintron CB, et al. Lack of hippocampal volume change in long-term heavy cannabis users. *American Journal on Addictions* 2005;14:64-72.
23. Meier, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Pro Natl Acad Sci* 012;109(40):2657-64.
24. DuPont R, et al. Drug driving research: A White Paper. Prepared for NIDA. Accessed November 2011 at *http://stopdruggeddriving.org/pdfs/druggeddrivingawhitepaper.pdf.*
25. Compton R & Berning A. Results of the 2007 National Roadside Survey of Alcohol and Drug Use by Drivers. Traffic safety facts research notes (DOT HS 811 175). Washington, DC: National Highway Traffic Safety Administration.
26. Crancer A & Crancer A. The involvement of cannabis in California fatal motor vehicle crashes. 1998-2008, June 2010. Accessed November 2011 at *http://druggeddriving.org/pdfs/CAMJStudyJune2010.pdf.*
27. Li M, Brady J, et al. Cannabis use and motor vehicle crashes. *Epidemiological Reviews*, in press.
28. Hayatbakhsh MR, Najman JM, et al. Cannabis and anxiety and depression in young adults: A large prospective study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2007;46(3):408-417.
29. Manrique-Garcia E, Zammit S, et al. Cannabis use and depression: a longitudinal study of a notional cohort of Swedish conscripts. *BMC Psychiatry* 2012;12:112.
30. Somaini, et al. Psychological responses to unpleasant emotions in cannabis users. *European Archives of Psychiatry and Clinical Neuroscience.* Jul 20 (Epub ahead of print).
31. Degenhardt L, Hall W, et al. The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. *Addiction* 2012; 10:1360-0443.
32. Hall W & Degenhardt L. Prevalence and correlates of cannabis use in developed and developing countries. *Current Opinion in Psychiatry* 2007;20:393-97.
33. Grech A, van Os, et al. Cannabis use and outcome of recent onset psychosis. *European Psychiatry* 2005;20:349-53.
34. Large M, et al. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch Gen Psychiatry* 2011;68(6):555-61.
35. Arseneault L, et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal* 2012;325:1212-1213.

References *continued*

36. Anthony JC, Warner LA, et al. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 2004;2(3):244-268.

37. Chen K, O'Brien MS, et al. Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000-2001. *Drug and Alcohol Dependence* 2005; 79(1):11-22.

38. Kokkevi A, Nic Gabhainn S, et al. Early initiation of cannabis use: a cross national European perspective. *Journal of Adolescent Health* 2006;39:712-19.

39. Compton W, Grant B, et al. Prevalence of cannabis use disorders in the U.S.: 1991-1992 and 2001-2002. *Journal of the American Medical Association* 2004;291:2114-2121.

40. SAMSHA. Office of Applied Studies. Treatment Episode Data Set (TEDS): 2009 Discharges from Substance Abuse Treatment Services, *DASIS* 2009.

41. Stephens RS, Roffman RA, et al. Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology* 1993; 61:1100-1104.

42. Stephens RS, Babor BF, et al. The Marijuana treatment project: Rationale, design and participant characteristics. *Journal of the American Medical Association* 2002;287:1123-31.

43. Budney AJ, Moore BA, et al. The time course and significance of cannabis withdrawal. *Journal of Abnormal Psychology* 2003;112:393-402.

44. Mayet A, Legleye S, et al. Cannabis use stages as predictors of subsequent initiation with other illicit drugs among French adolescents: use of a multi-state model. *Addict Behav* 2012;37(2):160-6.

45. Fried PA, Watkinson B, et al. Differential effects on cognitive functioning in 13 to 16 year olds parentally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 2003;25:427-36.

46. Richardson GA, Ryan C, et al. Prenatal alcohol and marijuana exposure effects on neuropsychological outcomes at 10 years. *Neurotoxicology and Teratology* 2002;24:309-320.

47. Aldington S, Williams M, et al. Effects of cannabis on pulmonary structure, function, and symptoms. *Thorax* 2007;62:1058-63.

48. Tetrault JM, et al. Effects of cannabis smoking on pulmonary function and respiratory complications: a systematic review. *Arch Intern Med* 2007;167:221-28.

49. Roth MD, Arora A, et al. Airway inflammation in young marijuana and tobacco smokers. *American Journal of Respiratory and Critical Care Medicine* 1998;157(3):928-37.

50. Barsky SH, Roth MD, et al. Histopathological and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. *Journal of the National Cancer Institute* 1998;90(16):1198-1205.

51. Jayanthi S, Buie S, et al. Heavy marijuana users showed increased serum apolipoprotein C-III levels: Evidence from proteomic analyses. *Molecular Psychiatry* 2010;15(1):101-112.

52. Daniel W, Bowles L, et al. The intersection between cannabis and cancer in the United States. *Critical Reviews in Oncology/Hematology* 2012;83(1):1-10.

53. Faggiono F, Vigna-Taglianti F, et al. School-based prevention for illicit drug use. The Cochrane Reviews, found December 2011 at *http://summaries.cochrane.org/CD003020/school-based-prevention-for-illicit-drugs-use,* 2008.

54. Gates S, McCambridge J, et al. Interventions for prevention of drug use by young people delivered in non-school settings. The Cochrane Review. Found December 2011 at *http://summaries.cochrane.org/CD005030/interventions-delivered-to-young-people-in-non-school-settings-for-the-prevention-of-drug-use.*

55. Budney A, Roffman R, et al. Marijuana dependence and its treatment. *Addiction Science and Clinical Evidence* 2007;4:4-18.

56. Roffman RA, Stephens RS. Cannabis dependence: its nature, consequences and treatment. Cambridge, UK: *Cambridge University Press,* 2006.

57. Miller WR & Rollnick R. Motivational Interviewing: Preparing People for Change (3rd edition). New York: *Guilford Press,* 2013.

58. Dennis M, Godley SH, et al. The Cannabis Youth Treatment (CYT) Study: Main findings from 2 randomized trials. *Journal of Substance Abuse Treatment* 2004;27:197-213.

59. Kilmer B, Caulkins JP, et al. Altered state? Assessing how cannabis legalization in California influence cannabis consumption and public budgets, *RAND,* 2010.

60. MacCoun R & Reuter P. Drug War Heresies: Learning from other vices, Times and Places. New York: *Cambridge University Press,* 2001.

61. Hall WD. A cautious case for cannabis depenalization. In M. Earlywine (ed.), Pot politics: Marijuana and the costs of prohibition (pp.91-112). New York: *Oxford University Press,* 2007.

62. Nunberg H, Kilmer B, et al. An Analysis of applicants presenting to a medical cannabis specialty practice in California. *Journal of Drug Policy Analysis* 2011;4 (1):Article 1.

63. Cerda M, et al. Medical cannabis laws in 50 states: Investigating the relationship between state legalization of medical cannabis and cannabis use, abuse, and dependence. *Drug and Alcohol Dependence* 2012;120(1-3):22-7.

64. Wall M, et al. Adolescent cannabis use from 2002-2008: Higher in states with medical cannabis laws, Cause still unclear. *Annals of Epidemiology* 2011;21(9):714-716.

ADDRESS CORRESPONDENCE TO:
Western Psychiatric Institute and Clinic of UPMC
3811 O'Hara St.
Pittsburgh, PA 15213
1-877-624-4100

Claudia Roth, PhD
President and CEO
Western Psychiatric Institute and Clinic of UPMC
Vice President
UPMC Behavioral Health

David A. Lewis, MD
Medical Director and Director of Research
Western Psychiatric Institute and Clinic of UPMC
UPMC Professor in Translational Neuroscience
Chairman, Department of Psychiatry
University of Pittsburgh School of Medicine

ONLINE CME OPPORTUNITIES

Adolescent Substance Use Disorders and Brain Development

Duncan Clark, MD, PhD, discusses the relationship between adolescent substance use disorders and teen brain development.

Suicide in Old Age: Risk and Management

Alexandre Y. Dombrovski, MD, provides an overview of how to assess and manage suicidal risk in older individuals.

Oxidative Stress, Omega-3 Fatty Acids, and Schizophrenia: An Integrative View

Jeffrey K. Yao, PhD, provides an overview for membrane pathology in schizophrenia as a function for oxidative stress and essential fatty acids.

UPMCPhysicianResources.com/ Psychiatry

A world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of accountable, cost-effective, patient-centered care. It provides more than $622 million a year in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution. The largest nongovernmental employer in Pennsylvania, UPMC integrates more than 60,000 employees, 20 hospitals, 400 doctors' offices and outpatient sites, a 2.2-million-member health insurance division, and international and commercial operations. Affiliated with the University of Pittsburgh Schools of the Health Sciences, UPMC ranks No. 10 in the prestigious *U.S. News & World Report* annual Honor Roll of America's Best Hospitals — and No. 1 in Pennsylvania. For more information, go to UPMC.com.

Western Psychiatric Institute and Clinic of UPMC

Integrating Clinical and Technological Innovation, Research, and Education

UPMC and its academic partner, the Department of Psychiatry of the University of Pittsburgh School of Medicine, constitute one of the leading centers for research and treatment of individuals who have challenging or particularly difficult mental health conditions and/or addictive disorders.

For more than 60 years, the integration of research, academia, and clinical services has infused best-practice research into clinical settings for the individuals who need it most.

We serve individuals across the lifespan, from young children to aging adults. Through our inpatient and outpatient continuum of care, we provide services for more than 30,000 individuals each year.

The Department of Psychiatry ranks near the top nationally in research funding received from the National Institutes of Health (NIH) including primary research grants from 12 different NIH institutes, such as the National Institute of Mental Health, the National Institute of Aging, and the National Institute of Drug Abuse.

© 2013 UPMC
USNW409882 HM 09/13