DH, MMRegulations

From: Shoemaker, Deborah <dshoemaker@pamedsoc.org>
Sent: Monday, April 5, 2021 6:48 PM
To: DH, MMRegulations
Subject: [External] Public Comments to MM Permanent regulations: comments and documentation enclosed
Attachments: PaPS comments on MM permanent regulations 421.pdf; Overview of High Potency THC.pdf; Higher Addiction with High Potency THC.pdf; FLORIDA BOARD OF MEDICINE medical-marijuana-consent-form.pdf

April 5, 2021

Hello Mr. Collins:

On behalf of the Pennsylvania Psychiatric Society, I am enclosing our formal comments, along with supportive documentation, during the public comment period on the Department's proposed permanent medical marijuana regulations.

We appreciate the opportunity to provide our member's clinical knowledge and expertise on this issue. Please do not hesitate to contact me with any questions or if you need any additional information. Have a wonderful week.

Deb

Take care and be safe-

Deborah Ann Shoemaker, Lobbyist and Ethics Specialist
Pennsylvania Psychiatric Society
400 Winding Creek Boulevard
Mechanicsburg, Pennsylvania 17050
Ph: 1.800.422.2900; direct: 717.909.2689
Cell: 717.575.9159
Email: dshoemaker@pamedsoc.org

Pennsylvania Psychiatric Society
The Pennsylvania District Branch of the American Psychiatric Association

400 Winding Creek Blvd
Mechanicsburg, PA
17050

(800) 422-2900
FAX (855) 918-3611
E-mail papsych@papsych.org
www.papsych.org

April 5, 2021

Mr. John J. Collins, Director
Office of Medical Marijuana
Pennsylvania Department of Health
Room 628, Health and Welfare Building
625 Forster Street
Harrisburg, PA 17120
Email: RA-DHMMregulations@pa.gov

Dear Mr. Collins:

On behalf of the Pennsylvania Psychiatric Society (PaPS), we are writing to comment on the problem with the currently approved serious medical conditions for medical marijuana in Pennsylvania:

1. Anxiety disorders;
2. Autism;
3. Opioid Use Disorder (OUD), for which conventional therapeutic interventions are contraindicated or ineffective, or for which adjunctive therapy is indicated in combination with primary therapeutic interventions; and
4. Post-Traumatic Stress Disorder (PTSD).

The diagnosis and treatment of these four conditions is part of psychiatric practice. The diagnosis and treatment of OUD also falls under the purview of addiction psychiatry and addiction medicine practice.

We are writing these comments as members of the Pennsylvania district branch of the American Psychiatric Association (APA). It is important that the commonwealth recognizes that the APA disagrees with the use of medical marijuana to treat any of the above listed conditions. Furthermore, the American Academy of Child and Adolescent Psychiatry (AACAP) opposes the use of medical marijuana in children and adolescents with Autism Spectrum Disorders. Both the American Academy of Addiction Psychiatry (AAAP) and the American Society of Addiction Medicine (ASAM) oppose the use of medical marijuana in patients with OUD.

There is no scientific evidence showing efficacy of medical marijuana sold in Pennsylvania dispensaries for any of these serious medical conditions. There are clear risks of harm for our patients using the medical marijuana sold in Pennsylvania state dispensaries for these conditions. We have many effective treatments which may be ignored based on the commonwealth's endorsement of a regimen unsupported by science.

We are also writing to comment on the dangers of PA Department of Health's failure to regulate the high concentration of THC in products sold at state medical marijuana dispensaries. We are getting reports from patients that they are not able to find products with less than 10% THC at the state dispensaries and that most products sold have 25% THC and higher, including 80% THC concentration products. In fact, most randomized controlled studies which have produced limited evidence have looked at ratios using CBD:THC formulas in a 20:1 ratio which is not the

same product found in dispensaries. There are clear risks of harm for our patients using medical marijuana with THC concentrations greater than 10%. A recent study conducted in Europe and Brazil 30.3% of cases of first-episode psychosis could be prevented in London and 50.3% of cases of first-episode psychosis could be prevented in Amsterdam. (Marta DiForti et al, *The Contribution of cannabis use to variation in the incidence of psychotic disorders across Europe (EU-GEI): Multicenter Case- Control Study*. The Lancet, Psychiatry, May 2019).

Another study conducted in England found that THC concentration of >15% is associated with greater severity of addiction. (Freeman TP, Winstock AR. *Examining the profile of high-potency cannabis and its association with severity of cannabis dependence.* Psychol Med 2015:45:3181-3189).

Suggested Changes to Reduce Patient Harm:

1. PA Department of Health can set a regulatory cap on the concentration of THC. Ideally this would be less than 10% as there is no good research on concentrations greater than this for any medical condition and there is significant literature on the negative effects of high potency THC.
2. PA Department of Health can follow the example of Florida and implement a regulatory mandate that a qualified physician must obtain a written medical marijuana consent form from a qualified patient. The Florida Board of Medicine Medical Marijuana Consent Form (attached) is a good example of a process implemented by the state of Florida to help ensure that appropriate information about lack of scientific evidence of efficacy for qualified conditions and information about known risks of harm to patients associated with medical marijuana use is fully disclosed to patients before they initiate use of medical marijuana. If the PA Department of Health were to use the Florida Board of Medicine Medical Marijuana Consent Form, this would provide an additional harm reduction strategy for the patients in our commonwealth.
3. Medical marijuana should appear on the Pennsylvania Prescription Drug Monitoring Program (PDMP) or another accessible database so physicians can safely prescribe other medications and have risk/benefit discussions with their patients about treatment options.

Thanks for the ability to present our thoughts during this public comment period. Do not hesitate to contact us with any questions or if you need additional information.

Sincerely,

Richard Silbert, MD, DLFAPA
PaPS President

Marina Goldman, MD, FAPA
PAMED/PaPS representative to DOH Marijuana Physician Work Group

Enclosures

The Problem with the Current High Potency THC Marijuana from the Perspective of an Addiction Psychiatrist

by Elizabeth Stuyt, MD

Advocates for the legalization of medical and retail marijuana are quick to point out all the possible benefits that a community might see from such a venture. These include increased jobs, increased tax revenue, possible medical benefits and they advertise it as "safe" and "healthy" and "organic." They utilize the words "cannabis" and "marijuana" for everything without differentiating between the different forms of cannabis that can have very different effects on the mind and body.

Many people who have voted for legalization thought they were talking about the marijuana of the 1960s to 1980s when the THC content was less than 2%. However, without any clear guidelines or regulations from government officials, the cannabis industry has taken a page from the tobacco and alcohol industries' play book and developed strains of marijuana and concentrated marijuana products with much higher concentrations of THC, the psychoactive component that causes addiction. The more potent a drug is, the stronger the possibility of addiction and the more likely the person will continue to purchase and use the product.

Elizabeth 'Libby' Stuyt, MD, is a board certified Addiction Psychiatrist and a Senior Instructor for the University of Colorado Health Science Program, Department of Psychiatry. She is the medical director for a 90-inpatient dual diagnosis treatment program in Pueblo, Colorado.
Contact: libbystuyt@msn.com

The active component in marijuana that people find so desirable was not really known until the 1960s when a research team in Israel found that after injecting THC into aggressive rhesus monkeys, they became calm and sedate.[1] This team discovered that there was a receptor in the brain that fit THC like a glove so they named these receptors cannabinoid receptors. It was not until the 1990s that this same team discovered why we have these receptors in our brain.[1] They discovered compounds produced by our bodies that fit into these receptors which they named anandamides, a Sanskrit word for "supreme joy." These receptors are found all over the brain and are still called endocannabinoid receptors but that is not because they are meant for people to take in THC.

The primary problem with the current available cannabis in dispensaries in Colorado is that the THC content is not like it used to be. Prior to the 1990s it was less than 2%. In the 1990s it grew to 4%, and between 1995 and 2015 there has been a 212% increase in THC content in the marijuana flower. In 2017 the most popular strains found in dispensaries in Colorado had a range of THC content from 17-28% such as found in the popular strain named "Girl Scout Cookie."[2] Sadly these plants producing high levels of THC are incapable of producing much CBD, the protective component of the plant so these strains have minimal CBD. For example the Girl Scout Cookie strain has only 0.09-0.2% CBD.

The flower or leaves that are generally smoked or vaped are only one formulation. We now have concentrated THC products such as oil, shatter, dab, and edibles that have been able to get the THC concentration upwards of 95%. There is absolutely no research that indicates this level of THC is beneficial for any medical condition. The purpose of these products is to produce a high, and the increased potency makes them potentially more dangerous and more likely to result in addiction.

Because there was initially no regulation on the edibles they have been made to look very similar to regular products that people consume such as chocolates, gummy bears, PopTarts etc. As a result there has been a significant increase in the accidental exposure/overdoses of children younger than nine in Colorado compared with the US at large.[3] New regulations beginning in 2019 require that all cannabis packaging in the state of Colorado must have a universal "THC" symbol on the label with the written warning "Contains Marijuana. Keep away from Children." All marijuana-infused products must have the universal symbol marked on at least one side of the "Standard Serving of Marijuana."

According to the 2014 Monitoring the Future Study, marijuana is by far the number one drug abused by eighth and twelfth graders.[4] Since legalization in Colorado, marijuana use in adolescents and those 18-25 has steadily climbed, well outpacing the national average. Colorado leads the nation in first time marijuana use by those aged 12-17, representing a 65% increase in adolescent use since legalization.[5] According to the Colorado Department of Public Health and Environment in 2015 the county of Pueblo, Colorado, has the highest prevalence of reported past month marijuana use by high school students at 30.1%.[6] It is well documented that when drugs are perceived as harmful, drug use decreases as we have seen with adolescent use of tobacco.[7] There is significantly less perception of harm by marijuana primarily because Colorado has normalized it as a society and allowed the perception that it is "organic" and "healthy" and that there is nothing wrong with it.

However, there are significant consequences of long-term or heavy marijuana use beginning in adolescence. Adolescence is a time of significant brain development. Normally during this period there is a significant increase in dopaminergic and glutamatergic stimulatory neurotransmitters and a decrease in serotonergic and GABAergic suppressive neurotransmitters located in the pre-frontal motor cortex – the last part of the brain to fully develop.[8] The prefrontal motor cortex or the "seat of judgement" is the last to fully develop and can take up to 25 – 30 years to fully develop. This equates to a great deal of learning, exploring and doing during this period, similar to stepping on the gas pedal and problems with impulse control and judgement, similar to problems stepping on the brake.

The reasons why adolescents are at such great risk for developing an addiction to drugs or alcohol is because this is a period with increased neurobiological based tendencies for risk taking with decreased suppressive and regulatory control, and this is a period of decreased parental monitoring and increase in peer affiliations, a "perfect storm."

The marijuana of old used to be classified as a hallucinogen and was thought to not cause addiction because there was no identified withdrawal syndrome. This has changed and with the increased potency of THC there is a definite recognized withdrawal syndrome which includes increased anger, irritability, depression, restlessness, headache, loss of appetite, insomnia and severe cravings for marijuana.[9] It has been reported that 9% of those who experiment with marijuana will become addicted; 17% of those who start using marijuana as teenagers will become addicted; and 25-50% of those who use daily will become addicted.[10] A 2015 study carried out in the UK found that high-potency cannabis use is associated with increased severity of dependence, especially in young people.[11]

Addiction is a problem with the learning and memory part of the brain and all drugs of abuse work in the same "reward pathway" where we learn to do anything such as eat and procreate. All drugs of abuse cause a release of dopamine from the nucleus acumbens that signifies salience and starts the process of long term potentiation which reinforces the learning. At the same time, the hippocampus which is vitally important for new memory and learning is negatively impacted by the chronic use of any addictive substance. These substances decrease neurogenesis in the hippocampus and actually cause shrinkage of the hippocampus and impair the ability to learn new things. This is true for alcohol, cocaine, methamphetamine, heroin, nicotine, and THC.[12] Animal studies have demonstrated impaired learning with all of these substances but the good news is that recovery is possible. When the use of addictive drugs is stopped and the animals are allowed to be in a recovery environment where they are free to exercise (voluntary exercise being one thing that improves neurogenesis) they can again learn new things.[13]

Human studies have shown that long-term (>10 years) and heavy (>5 joints per day) cannabis use compared with age matched non-using controls resulted in bilaterally reduced hippocampal and amygdala volumes ($p=.001$) and significantly worse performance on measures of verbal learning ($p<.001$).[14] There is evidence that recovery is possible in humans as well. A study of 40 male and 34 female long-term (@15 years) cannabis users versus 37 non-users, healthy controls divided the marijuana users into three groups; those that smoked predominantly THC in the previous three months, those who smoked a combination

of THC and CBD in the previous three months and former uses with a sustained abstinence of 29 months.[15] They found that cannabis users had smaller hippocampal volumes compared to controls but the users not exposed to CBD had an even greater (11%) reduced volumes (CBD appears to be somewhat protective). In the former users the hippocampal integrity was comparable to controls. The only problem with this study is they did not test for functional deficits to see if function improved along with hippocampal volume.

There are other important neurotransmitters that are very active during adolescence and include acetylcholine receptors (ACH) and endocannabinergic receptors (CB1). ACH helps us focus and concentrate and ACH innervation of the pre-frontal motor cortex reaches mature levels during adolescence.[16] These receptors in the brain are called nicotinic or nACHRs to differentiate them from the muscarinic receptors in the body. They are called nicotinic simply because nicotine binds to these receptors – not because we are supposed to use tobacco products. These receptors are involved in promoting or preventing neuronal cell death depending on the stage of brain development. Putting an exogenous form of nicotine in the developing brain, as in consuming tobacco, can dysregulate these fine tuning mechanisms during adolescence.

CB1 receptors regulate the balance between excitatory and inhibitory neuronal activity utilizing our own natural anandamides. Exposure to cannabis during adolescence disrupts glutamate which plays an important role in synaptic pruning in the pre-frontal motor cortex; disrupting normal brain development.[17] This is most likely why there are many studies demonstrating the negative effect on cognition and IQ in people who are exposed to marijuana beginning in utero through adolescence. In spite of this, nearly 70% of dispensaries in Denver, Colorado, recommend cannabis products to treat nausea in the first trimester of pregnancy.[18] This is basically bud-tenders practicing medicine without a license.

A study in New Zealand with a 20-year follow-up showed an average loss of 8 IQ points with early persistent teen use of marijuana.[19] If you already have a high IQ, a drop in 8 points may mean the difference between making As and making Bs, however for the person with an average IQ of 100 (50th percentile), a loss of 8 points can put that person in the 29th percentile with significant difficulty in functioning. A study out of Yale University tracked 1,142 students who achieved similar SAT scores and were enrolled in college.[20] They found that those who used minimal alcohol or cannabis had an average GPA of 3.1 at the end of the semester. Those who drank alcohol without using marijuana had an average GPA of 3.03 and those who used both alcohol and marijuana had an average GPA of 2.66.

Marijuana use is also correlated with creating or worsening many mental health problems including anxiety, depression, psychosis, and suicidal ideation. A prospective study in Australia followed 1,600 girls for seven years starting before they expressed symptoms of mental illness or substance abuse.[21] They found that girls who used marijuana at least once a week were twice as likely to develop depression than those who did not use, and those who used marijuana every day were five times more likely to suffer from depression and anxiety than non-users. A study of 307 adults with depression assessed symptoms, functioning and marijuana use at baseline, and three- and six-month intervals.[22] Researchers found that marijuana use was associated with poor recovery. Those aged 50+ increased their marijuana use compared to the youngest age group ($p<.001$) and the marijuana use worsened depression ($p<.001$) and anxiety ($p=.025$) symptoms. Marijuana use led to poorer mental health functioning compared to those who did not use marijuana ($p=.01$).

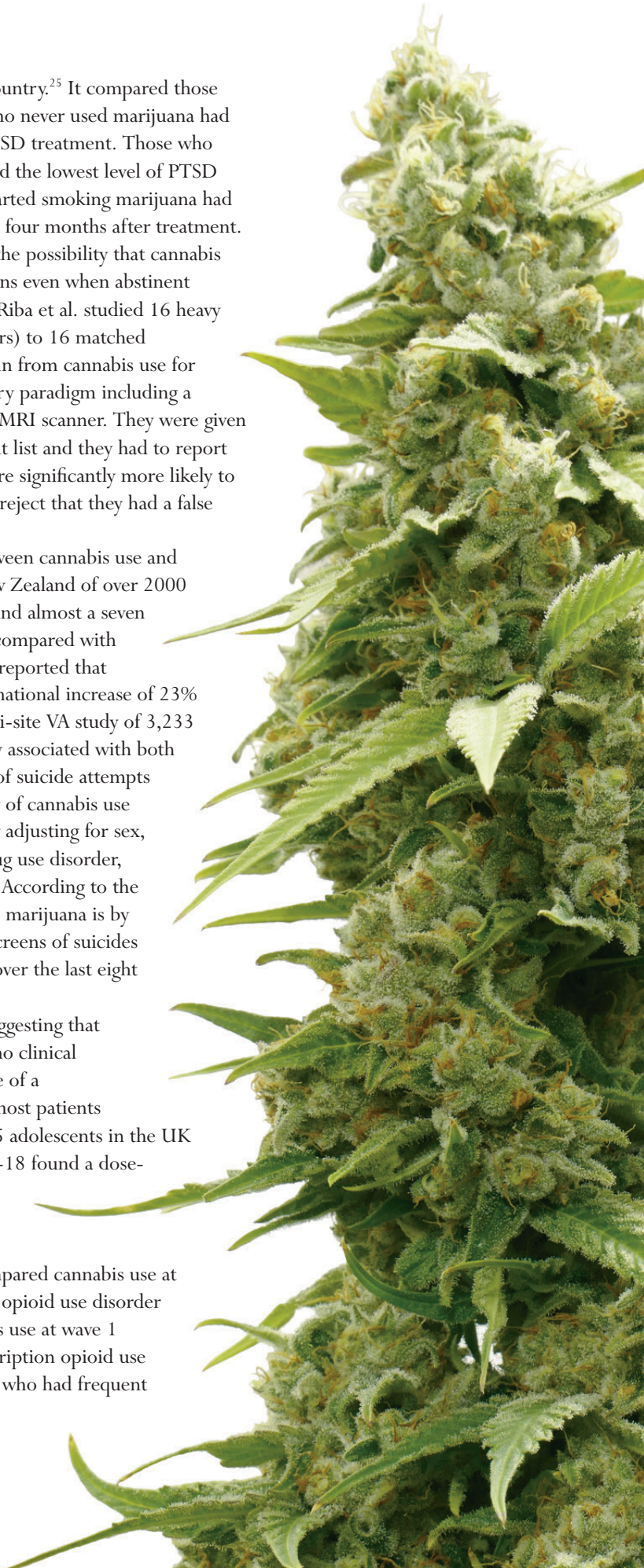
Numerous studies have demonstrated that using cannabis prior to the age of 15-18 significantly increases the risk of developing psychotic symptoms.[23] The risk is dose dependent and increases with greater frequency of use and with higher potency THC. A landmark study out of the UK analyzed 780 adults, ages 18-65, 410 with their first psychotic episode versus 370 matched healthy controls.[24] They found that use of high potency THC >15% resulted in a three times increased risk of psychosis, and if the use was daily there was a five times increased risk. Those using hash with <5% THC did not exhibit psychotic symptoms.

A growing number of states have identified PTSD as an approved condition for medical marijuana. However, this is not based on any research. There is no evidence that marijuana successfully treats PTSD and there is evidence that it can make it worse. Marijuana is not the answer for PTSD similar to the reason why benzodiazepines or alcohol are not the answer for PTSD. All these compounds do is provide temporary relief by numbing the individual and disconnecting them from the traumatic emotion. It does not resolve the trauma, and they have to continue to use multiple times a day in order to continue with the benefit. This can lead to increased addiction potential and withdrawal symptoms, cognitive impairment, a-motivational syndrome, and the potential for psychosis or worsening psychosis from the PTSD. An observational study done by the VA followed 2,276 Veterans who were treated for PTSD

in one of the VA PTSD treatment programs around the country.[25] It compared those using marijuana and those not using it and found those who never used marijuana had significantly lower symptom severity four months after PTSD treatment. Those who were using marijuana but stopped using it in treatment had the lowest level of PTSD symptoms four months after treatment, and those who started smoking marijuana had the highest levels of violent behavior and PTSD symptoms four months after treatment. Another conundrum that impacts treatment for PTSD is the possibility that cannabis users have an increased susceptibility to memory distortions even when abstinent and drug free which can compromise reality monitoring. Riba et al. studied 16 heavy cannabis users (daily for last two years – average of 21 years) to 16 matched cannabis naïve controls.[26] The cannabis users had to abstain from cannabis use for four weeks prior to the study. The study involved a memory paradigm including a study phase and a testing phase with the participant in an MRI scanner. They were given lists of four words to memorize and then shown a different list and they had to report if the words were on the previous list. Marijuana users were significantly more likely to have false recognition of the words and were less likely to reject that they had a false memory compared with the non-users.

Multiple studies have documented a relationship between cannabis use and suicidality. A large, longitudinal study in Australia and New Zealand of over 2000 adolescents and maximum frequency of marijuana use found almost a seven fold increase in suicide attempts in daily marijuana users compared with non-users.[27] A Congressional Hearing on April 27, 2017, reported that Veteran suicides were up 32% since 2001 compared to a national increase of 23% during the same time period. A 2017 cross-sectional multi-site VA study of 3,233 Veterans found that cannabis use disorder was significantly associated with both current suicidal ideation ($p<.0001$) and lifetime history of suicide attempts ($p<.0001$) compared to Veterans with no lifetime history of cannabis use disorder.[28] This significant difference continued even after adjusting for sex, PTSD, depression, alcohol use disorder, non-cannabis drug use disorder, history of childhood sexual abuse, and combat exposure. According to the Colorado Department of Public Health and Environment, marijuana is by far the most frequently encountered drug on toxicology screens of suicides among adolescents ages 10 – 19 and has been increasing over the last eight years.[29]

Misguided marijuana advocates have recently been suggesting that marijuana is a solution for the opioid epidemic. There is no clinical evidence of this and in fact, marijuana is found to be more of a "companion" drug rather than an "alternative" drug for most patients seeking addiction treatment in Colorado. A study of 5,315 adolescents in the UK with three or more measures of cannabis use from age 13-18 found a dose-response relationship between cannabis use trajectories in adolescence and nicotine dependence, harmful alcohol consumption, and other illicit drug use by age 21.[30] A large study of 34,653 individuals using NESARC data compared cannabis use at wave 1 (2001-2002 – 81% response rate) to prescription opioid use disorder at wave 2 (2004-2005 – 70.2% response rate).[31] Cannabis use at wave 1 was associated with a significant increase of having a prescription opioid use disorder at wave 2, with over four times the risk for those who had frequent use of marijuana.



There is evidence that prenatal exposure of cannabis can alter opioid gene function in humans. Fetal brains obtained from aborted fetuses from women who were using marijuana during their pregnancy were compared to those from women not using marijuana during pregnancy.[32] The researchers discovered impaired opioid-related genes in distinct brain circuits that they hypothesized may have long term effects on cognitive and emotional behavior. These findings are comparable to findings with animals. One study of prenatal cannabis exposure in rats found that the THC exposed rats exhibited shorter latency to first active lever press for heroin and had higher heroin-seeking during mild stress and drug extinction than animals not exposed to THC.[33] The THC exposed animals exhibited allostatic changes in the limbic encephalin systems in adulthood.

Another interesting study that supports the idea that cannabis use and opioid use are linked was in a randomized, double-blind, placebo controlled trial of naltrexone in non-treatment seeking cannabis smokers.[34] In a laboratory setting those receiving a placebo had 7.6 times the odds of self-administering active cannabis compared with those receiving daily naltrexone, an opioid receptor blocker.

If states continue to commercialize marijuana as has been done in Colorado we are destined to see many more people requiring treatment for addiction, depression, anxiety, suicidal ideation, and psychosis. We need to continually educate every one of the risks and increase prevention efforts to prevent children and adolescents from initiating marijuana use. This should include a strong ban on any advertising that appears to be directed toward youth – for all drugs including marijuana, tobacco, and alcohol. States will need to commit to increased funding for and availability of treatment options. The strongest recommendation would be to initiate regulations to limit the concentration of THC. Ideally this would be to less than 10% as there is no good research on concentrations greater than this for any medical condition and there is significant literature on the negative effects of high potency THC.

References

1. Sides H. Science seeks to unlock marijuana secrets. National Geographic Magazine. June 2015
2. www.leafly.com – accessed July 15, 2017
3. Wang GS et al. Unintentional pediatric exposures to marijuana in Colorado, 2009-2015. JAMA Pediatr.2016;170(9):e160971.
4. University of Michigan, 2014 Monitoring the Future Study http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2014.pdf
5. Rocky Mountain High Intensity Drug Trafficking Area. Marijuana in Colorado: the impact. 2017;5http://www.rmhidta.org/html/FINAL%202017%20Legalization%20of%20Marijuana%20in%20Colorado%20The%20Impact.pdf
6. Colorado Department of Public Health and Environment. Healthy Kids Survey. 2015 https://www.colorado.gov/pacific/sites/default/files/PF_Youth_HKCS_MJ-Infographic-Digital.pdf
7. University of Michigan, 2013 Monitoring the Future Survey, NIDA https://www.drugabuse.gov/publications/drugfacts/monitoring-future-survey-high-school-youth-trends
8. Schepis et al. Neurobiological Processes in Adolescent Addictive Disorders. Am J Addictions. 2008;17:6-23
9. Bonnet U, Preuss UW. The cannabis withdrawal syndrome: current insights. Sub Abuse Rehab 2017;8:9-37.
10. Volkow ND et al. Adverse Health Effects of Marijuana Use. N Engl J Med 2014;370:2219-2227.
11. Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. Psychol Med 2015:45:3181-3189.
12. Chambers RA. Adult hippocampal neurogenesis in the pathogenesis of addiction and dual diagnosis disorders. Drug Alcohol Depend 2013;130:1-12.
13. Mandyam CD, Koob GF. The addicted brain craves new neurons: putative role for adult-born progenitors in promoting recovery. Trends Neurosci 2012;35:250-260.
14. Regional brain abnormalities associated with long-term heavy cannabis use. Arch Gen Psychiatry 2008;65:694-701.
15. Yucel et al. Hippocampal harms, protection and recovery following regular cannabis use. Transl Psychiatry 2016;6:e710
16. deBry SC, Tiffany ST. Tobacco-induced neurotoxicity of adolescent cognitive development (TINACD): A proposed model for the development of impulsivity in nicotine dependence. Nicotine & Tobacco Research 2008; 10:11-25.
17. Lubman et al. Cannabis and adolescent brain development. Pharmacology and Therapeutics 2015;148:1-16
18. Dickson B et al. Recommendations from cannabis dispensaries about first-trimester cannabis use. Obstetrics and Gynecology 2018;131:10311038.
19. Meier MH et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. PNAS 2012; E2657-E2664. doi/10.1073/pnas.1206820109
20. Meda SA et al. Longitudinal influence of alcohol and marijuana use on academic performance in college students PLOS ONE | DOI:10.1371/journal.pone.0172213 March 8, 2017
21. Patton GC et al. Cannabis use and mental health in young people: cohort study. BMJ;2002:325:1195-1198.
22. Bahorik AL et al. Patterns of marijuana use among psychiatry patients with depression and its impact on recovery. J Affect Disord. 2017; 2013:168-171.
23. Pierre JM Risks of increasingly potent Cannabis: the joint effects of potency and frequency. Current Psychiatry 2017;16:14-20
24. DiForti et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis : a case-control study. Lancet Psychiatry, 2015; doi.org/10.1016/S2215-0366(14)00117-5.
25. Wilkinson et al. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. J Clin Psychology 2015;76:9.
26. Riba et al. Telling true from false: cannabis users show increased susceptibility to false memories. Molecular Psychiatry 2015;20:772-777.
27. Silins E et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. Lancet Psychiatry 2014;1:286-293.
28. Kimbrel NA et al. Cannabis use disorder and suicide attempts in Iraq/Afghanistan-era veterans J Psychiatric Research 2017:89;1-5.
29. https://www.colorado.gov/pacific/sites/default/files/CHED_VS_Health-Watch-No-94-Adolescent-Suicide-in-Colorado-2008-2012_0817.pdf
30. Taylor M et al. Patterns of cannabis use during adolescence and their association with harmful substance use behavior: findings from a UK birth cohort. J Epidemiol Community Health. 2017; 0:1–7. doi:10.1136/jech-2016-208503.
31. Olfson M et al. Cannabis use and risk of prescription opioid use disorder in the United States. AJP in Advance (doi:10.1176/appi.ajp.2017.17040413).
32. Wang et al. Prenatal exposure of cannabis alters opioid gene function in humans. Pharmacogenomics J, 2006;6:255-264.
33. Sapano et al. Prenatal cannabis exposure increases heroin seeking in adult rats. Biol Psychiatry 2007;61:554-563.
34. Haney et al. Naltrexone maintenance decreases cannabis self-administration and subjective effects of daily cannabis use. Neuropsychopharmacology 2015.

MM

Psychological Medicine (2015), **45**, 3181–3189. © Cambridge University Press 2015
doi:10.1017/S0033291715001178

ORIGINAL ARTICLE

Examining the profile of high-potency cannabis and its association with severity of cannabis dependence

T. P. Freeman[1]* and A. R. Winstock[2]

[1] *Clinical Psychopharmacology Unit, University College London, London, UK*
[2] *Institute of Psychiatry, King's College London, Camberwell, UK*

Background. Cannabis use is decreasing in England and Wales, while demand for cannabis treatment in addiction services continues to rise. This could be partly due to an increased availability of high-potency cannabis.

Method. Adults residing in the UK were questioned about their drug use, including three types of cannabis (high potency: skunk; low potency: other grass, resin). Cannabis types were profiled and examined for possible associations between frequency of use and (i) cannabis dependence, (ii) cannabis-related concerns.

Results. Frequent use of high-potency cannabis predicted a greater severity of dependence [days of skunk use per month: $b = 0.254$, 95% confidence interval (CI) 0.161–0.357, $p < 0.001$] and this effect became stronger as age decreased ($b = -0.006$, 95% CI −0.010 to −0.002, $p = 0.004$). By contrast, use of low-potency cannabis was not associated with dependence (days of other grass use per month: $b = 0.020$, 95% CI −0.029 to 0.070, $p = 0.436$; days of resin use per month: $b = 0.025$, 95% CI −0.019 to 0.067, $p = 0.245$). Frequency of cannabis use (all types) did not predict severity of cannabis-related concerns. High-potency cannabis was clearly distinct from low-potency varieties by its marked effects on memory and paranoia. It also produced the best high, was preferred, and most available.

Conclusions. High-potency cannabis use is associated with an increased severity of dependence, especially in young people. Its profile is strongly defined by negative effects (memory, paranoia), but also positive characteristics (best high, preferred type), which may be important when considering clinical or public health interventions focusing on cannabis potency.

Received 9 January 2015; Revised 18 May 2015; Accepted 19 May 2015; First published online 27 July 2015

Key words: Addiction, cannabidiol, cannabis, delta-9-tetrahydrocannabinol, dependence, marijuana.

Introduction

There is huge variation in the types of cannabis (marijuana) available worldwide (UNODC, 2014). This is evident in illicit markets and also legal ones. For example, an unprecedented number of cannabis products and preparations are now available in Colorado (Coombes, 2014). By contrast, sales in Uruguay may be restricted to five strains only, with an upper limit on potency (Coombes, 2014).

Cannabis potency is typically judged according to concentrations of delta-9-tetrahydrocannabinol (THC), the primary psychoactive constituent in cannabis. However, the cannabis plant contains many other cannabinoids, most notably cannabidiol (CBD). These other cannabinoids (and possibly other plant chemicals known as terpenoids; Russo, 2011) contribute to potency by moderating the effects of THC. For example, CBD can block or dampen the effects of THC across a range of domains (Zuardi *et al.* 1982; Morgan & Curran, 2008; Morgan *et al.* 2010*a*,*b*, 2012; Englund *et al.* 2012; Hindocha *et al.* 2015). These findings concur with users' ratings of cannabis potency, which are positively correlated with THC and negatively with CBD (Freeman *et al.* 2014).

Natural cannabinoid synthesis (and therefore cannabis potency) is influenced by a range of factors including genetics, growing conditions (especially light), harvest time, the part of the plant used, drying, storing and processing (Potter, 2014). Most products can be classified into three broad types: (1) high potency – indoor-grown floral material of unfertilized plants, whereby energy is diverted from seed production to cannabinoid synthesis ('skunk', 'sinsemilla'; meaning 'without seeds'); (2) low potency – outdoor-grown imported floral material ('herbal', 'grass', 'weed'); and (3) compressed blocks of plant matter ('resin', 'hashish'). Skunk is characterized by the highest THC content (~15%), followed by imported herbal/grass (~9%) and then resin (~5%), although there is considerable variation within these categories (Hardwick & King, 2008). Concentrations of CBD are

* Address for correspondence: Dr T. Freeman, Clinical Psychopharmacology Unit, University College London, Gower St, London, WC1E 6BT, UK.
(Email: tom.freeman@ucl.ac.uk)

typically low or completely absent in skunk and other herbal/grass preparations. By contrast, resin/hashish (and presumably landrace populations of cannabis plants) typically contain comparable quantities of THC and CBD (Potter *et al.* 2008). Thus, indoor-grown floral cannabis (skunk) is the clearly most potent type of cannabis (followed by imported herbal/grass, and then resin/hashish), and might be expected to be most strongly associated with any adverse effects of cannabis use. This is currently an under-researched area, although preliminary evidence suggests that regular use of high-potency (skunk) cannabis is predictive of first-episode psychosis (Di Forti *et al.* 2009) and an earlier onset of psychosis, particularly among daily users (Di Forti *et al.* 2013). By contrast, resin/hashish is not linked to an increased risk of psychosis, even among daily users (Di Forti *et al.* 2015).

It is estimated that 3.8% of the world's population used cannabis in the last year (UNODC, 2014) and this figure has remained relatively stable in the last decade. In England and Wales, however, prevalence of last year use dropped from 10.7% to 6.6% between 2002/2003 and 2013/2014 (Home Office, 2014). Despite this overall reduction in use, demand for cannabis in addiction-treatment services has continued to rise across the same time period: between 2005/2006 and 2013/2014 new admissions for cannabis rose from 7579 to 11 821 in adults (NDTMS, 2014) and from 9043 to 13 659 among under 18s (NDTMS, 2015). There are now more first-time clients for cannabis treatment in Europe than any other illicit drug (EMCDDA, 2014).

One possible explanation for these trends is an increase in cannabis potency. Data from cannabis seizures have documented rising THC concentrations in the UK. This is predominantly due to an increase in the availability of high-potency, indoor-grown (skunk) cannabis which made up 15% of police seizures in 1999–2002 (King *et al.* 2004), 55% in 2004–2005 (Potter *et al.* 2008) and 81% in 2007–2008 (Hardwick & King, 2008). These trends are matched by seizure data across Europe (EMCDDA, 2014). Cannabis users titrate (use less) as THC rises but only partially (Freeman *et al.* 2014; van der Pol *et al.* 2014) and not in response to CBD (Freeman *et al.* 2014). It is therefore possible that repeated exposure to high THC concentrations, and little if any CBD, may have increased users' dependence on cannabis.

In this study, we recorded detailed information on use of and experiences with different types of cannabis through an online drug survey. This approach made it possible to recruit a large sample who had used all of three different cannabis types (skunk, other grass, resin) within the last 12 months, permitting within-subject comparison of cannabis types. We aimed to test the hypothesis that severity of dependence, and concerns about cannabis use, are more strongly associated with use of high-potency than low-potency cannabis. Additionally, we explored users' experiences of each type of cannabis in relation to effects on memory, paranoia, quality of high, preference, value for money and availability.

Method

Design and participants

An online cross-sectional drugs survey, The Global Drug Survey, was conducted in November 2009 as reported elsewhere (Winstock *et al.* 2011). All participants confirmed that they were aged $\geqslant$18 years, and consented for the information they gave to be analysed. Ethical approval was received from the joint South London and Maudsley and Institute of Psychiatry National Health Service (NHS) Research Ethics Committee.

Assessments

The survey collected demographic data and detailed information on use of and experience with a number of substances. The data presented and analysed in this report is the UK data only; cases living in England, Scotland, Wales, and Northern Ireland form the UK dataset. Rather than recording information on cannabis use generally (e.g. age when cannabis was first used, days of cannabis use per month), separate questions were provided for (1) resin, (2) skunk grass (hereafter 'skunk'), (3) grass other (hereafter 'other grass'). This enabled each type to be rated as a separate drug. The following information was collected for each type of cannabis:

Comparing use of cannabis types

Used in the last 12 months? (yes/no).
Days used in the last month.
How long does ⅛th last you (in days).†
How many joints from ⅛th?

Profiling cannabis types

Respondents who had used all three cannabis types in the last 12 months were asked to choose one type for each of the following questions:

Which gives the best high?
Which is the best value for money?
Which is most likely to get you paranoid?

† One-eighth of an ounce (3.5 g), an amount typically sold in the UK.

Which is most likely to affect your memory?
Which is your preferred type?
Which is most available?

Route of administration

Respondents were asked whether they had ever used cannabis using the following methods: smoked in joint without tobacco, smoked in joint with tobacco, smoked in bong/water pipe without tobacco, smoked in bong/water pipe with tobacco, eaten/cooked, used in a vaporizer.

Severity of dependence and cannabis-related concerns

These questions were assessed with reference to cannabis use generally. Cannabis dependence was assessed using the Severity of Dependence Scale (SDS; Gossop *et al.* 1995), which was adapted for the survey with abbreviated response options as shown below. Scores can range from 0 to 15, and scores $\geqslant 3$ on the original scale indicate dependence on cannabis (Swift *et al.* 1998).

(1) Do you ever think your use of cannabis is out of control? [never (0); sometimes (1); often (2); always (3)].
(2) Does the prospect of missing a smoke make you very anxious or worried? [never (0); sometimes (1); often (2); always (3)].
(3) Do you worry about your use of cannabis? [never (0); sometimes (1); often (2); always (3)].
(4) Do you wish you could stop? [never (0); sometimes (1); often (2); always (3)].
(5) How difficult would you find it to stop or go without? [not difficult (0); quite difficult (1); very difficult (2); impossible (3)].

Additionally, the following questions were asked (yes/no):

Have you ever discussed your cannabis use with a healthcare professional?
Have you ever thought you might need treatment for your cannabis use?
Have you ever sought treatment for cannabis use?
Have you ever tried to stop smoking cannabis?

Participants were also asked about a range of concerns relating to their cannabis use:

We are interested in what worries you about smoking cannabis. Please rate the following possible health-related consequences of smoking cannabis on a scale of 1–10, where 1 = no concern for you and 10 = big concern for you: cancer, chronic lung disease, effect on memory, effect on mental health, legal issues, effect on relationships, effect on work or study, lack of motivation.

Statistical analysis

Repeated-measures ANOVA models were used to compare each cannabis type for indices of use. *Post-hoc t* tests were corrected locally using the Bonferroni method. χ^2 tests were used for comparing the profile of cannabis types. Current age was split into quartiles (<21, 21–22, 23–27 and >27 years) for analysis of first use, and profile of effects. Pearson correlational analyses were used to establish associations between cannabis use variables and SDS scores. Multiple regression was used to predict severity of cannabis dependence and cannabis-related concerns from indices of cannabis use. Analysis of gender was coded as female = 1, male = 2, and age was entered as a continuous variable. For all regression models, bias-corrected accelerated 95% confidence intervals (CIs) were estimated using 10 000 boostrapping samples.

Results

Demographics

Data were available for 2514 respondents. In the last year, prevalence of use was 72.5% for skunk, 68.6% for other grass, and 58.7% for resin cannabis preparations. Thirty-seven per cent (929 respondents) had used all three cannabis preparations in the last year; all further analyses were conducted in this sample. These participants had a mean age of 24.25 (S.D.=6.86) years and 70.2% were male. Routes of administration (ever used/most common use) were as follows: smoked in joint with tobacco (98.9%/85.2%), smoked in joint without tobacco (75.5%/5.5%), smoked in bong/water pipe with tobacco (69.6%/3.3%), smoked in bong/water pipe without tobacco (85.2%/4.5%), eaten/cooked (80.1%/1.1%), used in a vaporizer (36.8%/0.4%).

Comparing use of cannabis types (Table 1)

Participants reported differences in the number of days they had used each type of cannabis in the last month ($F_{2,761} = 38.332$, $p < 0.001$, $\eta^2_p = 0.087$). Skunk was used for more days than other grass ($p < 0.001$) and resin ($p < 0.001$), while other grass was used for more days than resin ($p < 0.001$). No differences were found for the number of days to smoke ⅛th ($F_{2,895} = 1.655$, $p = 0.197$, $\eta^2_p = 0.003$). Differences emerged for the number of joints made out of ⅛th ($F_{2,893} = 62.710$, $p < 0.001$, $\eta^2_p = 0.108$), reflecting a larger number of joints made from resin compared to skunk ($p < 0.001$) or other grass ($p < 0.001$); a similar number of joints were made for skunk and other grass ($p = 0.078$). There were also differences in age of first use ($F_{2,1432} = 41.059$, $p < 0.001$, $\eta^2_p = 0.043$); resin was used earlier than skunk ($p < 0.001$)

Table 1. *Comparing use of three cannabis types*

	Skunk	Other grass	Resin
Days used in the last month[a]	14.05 (10.68)	11.46 (10.43)	9.45 (9.90)
Days taken to smoke 3.5 g	8.55 (29.28)	7.31 (24.49)	8.14 (19.80)
Number of joints made out of 3.5 g[a]	7.93 (5.12)	7.63 (4.87)	9.41 (5.70)
Age first used[a]	15.90 (3.70)	15.38 (2.55)	15.18 (2.67)

Values given are mean (S.D.) scores.
[a] Difference across cannabis types at $p < 0.001$.

and other grass ($p = 0.002$); while other grass was used earlier than skunk ($p < 0.001$).

The later age of skunk onset might be attributable to its low availability at the time when this sample first tried cannabis (e.g. 15% prevalence in 1999–2002; King *et al.* 2004). We explored this possibility by adding a between-subject factor of current age, split into quartiles, into the model (see Fig. 1). This revealed a cannabis type × age interaction ($F_{5,1468} = 29.456$, $p < 0.001$, $\eta^2_P = 0.089$) as well as effects of cannabis type ($F_{2,1468} = 53.598$, $p < 0.001$, $\eta^2_P = 0.056$) and age ($F_{3,900} = 42.331$, $p < 0.001$, $\eta^2_P = 0.124$). *Post-hoc* tests showed that in young people (under 21's and 21- to 22-year-olds), all three types of cannabis were first tried at similar ages (all p's > 0.06). By contrast, 23- to 27-year-olds had tried resin earlier than other grass ($p < 0.001$) and skunk ($p = 0.010$), which were both tried at an equivalent age ($p = 1.000$). In the over 27's, there was a marked delay in first trying skunk relative to other grass (2.00 years, $p < 0.001$) and resin (2.42 years, $p < 0.001$), and resin was again tried earliest ($p = 0.002$ compared to other grass). These data are consistent with a shift in the relative availability of resin and skunk over time, alongside a tendency for younger people to try cannabis at an earlier age.

Profiling cannabis types (Fig. 2)

Ratings differed across the three cannabis types for 'best high' ($\chi^2_2 = 539.919$, $p < 0.001$), 'value for money' ($\chi^2_2 = 126.788$, $p < 0.001$), 'most likely to get you paranoid' ($\chi^2_2 = 719.880$, $p < 0.001$), 'most likely to affect your memory' ($\chi^2_2 = 838.049$, $p < 0.001$), 'preferred type' ($\chi^2_2 = 246.739$, $p < 0.001$), and 'most available' ($\chi^2_2 = 360.622$, $p < 0.001$). As shown in Fig. 1, skunk scored the highest for 'best high', 'most likely to get you paranoid', 'most likely to affect your memory', 'preferred type', 'most available'. Among these, resin scored above other grass for 'best high' ($\chi^2_1 = 7.879$, $p = 0.005$), 'most likely to get you paranoid' ($\chi^2_1 = 18.447$, $p < 0.001$) and 'most likely to affect your memory' ($\chi^2_1 = 44.445$, $p < 0.001$). By contrast, resin scored lower than other grass for 'most available' ($\chi^2_1 = 30.201$, $p < 0.001$) and they both scored equally for 'preferred type' ($\chi^2_1 = 1.011$, $p = 0.315$). In terms of 'value for money', resin was rated the highest, above skunk ($\chi^2_1 = 15.334$, $p < 0.001$), which in turn scored higher than other grass ($\chi^2_1 = 58.911$, $p < 0.001$). The same pattern of results was found when the sample was split according to gender or age quartiles.

Severity of dependence and cannabis-related concerns

Exploratory correlations were conducted between SDS scores and all 12 indices of use (for skunk, other grass and resin: age of first use, days used in the last month, days taken to smoke ⅛th, number of joints from ⅛th). For days used in the last month, Pearson's r values reflected a medium-large effect size for skunk ($r = 0.432$) and small-medium effect sizes for other grass ($r = 0.290$) and resin ($r = 0.247$). For all other indices of use, effect sizes were small (all r's $\leqslant 0.155$). Scores for severity of dependence (and individual concerns about cannabis) were therefore regressed onto days of skunk, other grass, and resin use in the last month.

Four hundred and three respondents had used each of the three cannabis types at least once in the last month; the following analyses were conducted in those individuals. Within their lifetime, 23.0% had discussed their cannabis use with a healthcare professional, 17.8% thought they might need treatment for their cannabis use, 5.3% had sought treatment for cannabis use, and 47.4% had tried to stop smoking cannabis. On the SDS, they had a mean score of 2.82 (S.D. = 3.29). Scores ranged from 0 to 14 (out of a maximum of 15) and quartiles were 0.00, 2.00, and 4.50. When classified using the cut-off of $\geqslant 3$ (Swift *et al.* 1998), 38% of the sample currently met criteria for cannabis dependence.

As shown in Table 2, frequency of cannabis use in the last month predicted severity of dependence, accounting for 14.4% of the variance in these scores. This was driven by skunk; no associations emerged for other grass or resin. We additionally investigated whether this effect was moderated by gender or age. Adding gender and age into the model (step 2) did not account for additional variance, but including them as moderators of skunk use (step 3) improved model fit. Removing redundant predictors (step 4) did not result in a loss of variance explained and accounted for a total of 15.5%. SDS scores increased ($b = 0.254$, 95% CI 0.161–0.357, $p < 0.001$) for each additional day of skunk per month. This relationship became stronger as age decreased ($b = -0.006$, 95% CI −0.010 to −0.002, $p = 0.004$). SDS scores also increased with age ($b = 0.081$, 95% CI 0.014–0.170, $p = 0.039$).

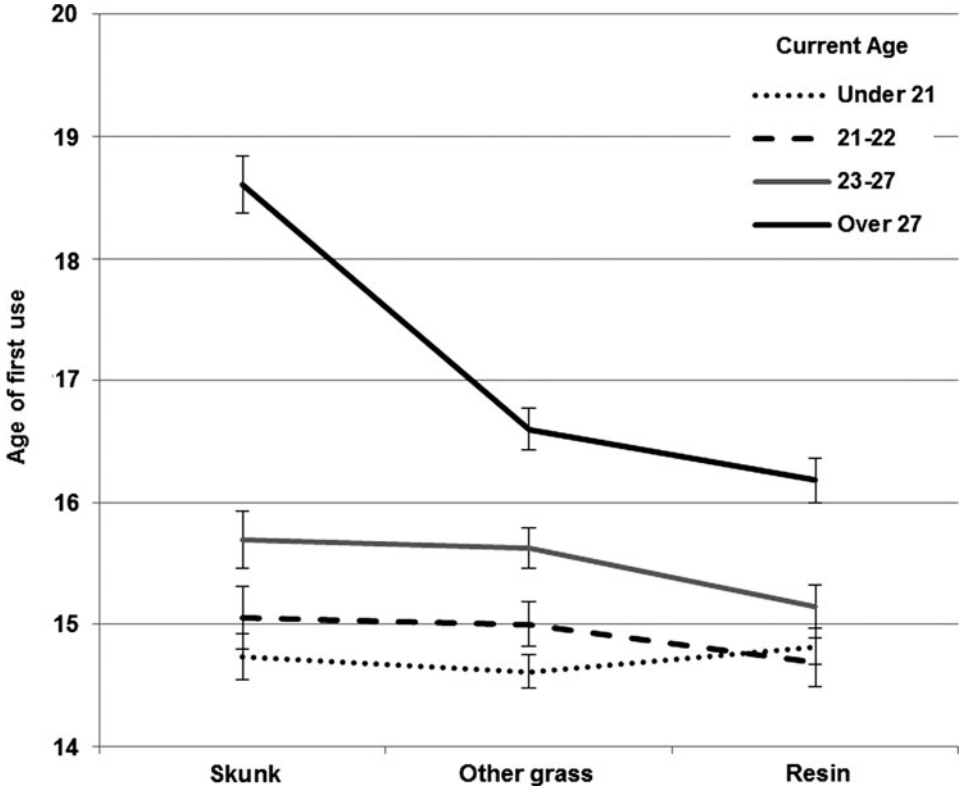


Fig. 1. Current age and first use of cannabis. Young people in the sample (currently under 23) were exposed to all three types of cannabis at similar ages. Older people were exposed to resin earlier than other types of cannabis, and skunk use was markedly delayed in the over 27's. These results support a shift in the relative availability of resin and skunk over time.

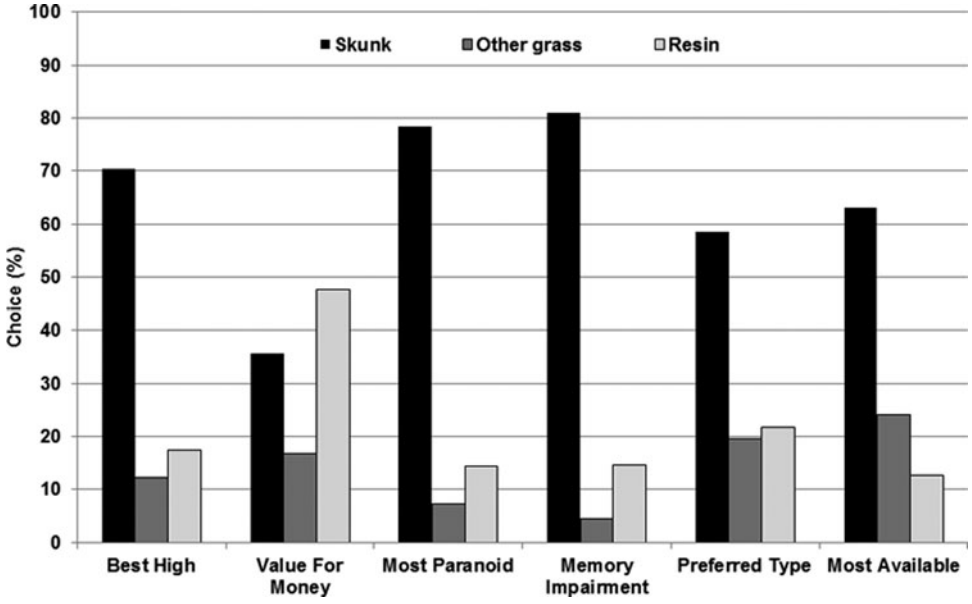


Fig. 2. Characteristics of three cannabis types. Skunk was the predominant choice for all attributes apart from value for money.

Mean (S.D.) scores for cannabis-related concerns about cannabis were as follows (presented in descending order of concerns). Memory: 4.98 (2.87); work or study: 4.58 (2.98); mental health: 4.42 (3.16); motivation: 3.97 (3.50); chronic lung disease: 3.85 (2.76); cancer: 3.70 (2.75); relationships: 3.33 (2.71); legal issues: 3.01 (2.66). Frequency of cannabis use (skunk, other grass, resin) did not predict scores for any of these concerns.

Table 2. *Predicting severity of cannabis dependence from frequency of use*

	b	95% CI		*p*
		Lower	Upper	
Step 1				
Total $R^2 = 0.144$, $p < 0.001$				
Constant	1.046	0.636	1.473	
Skunk	**0.093**	**0.048**	**0.139**	**<0.001**
Other grass	0.020	−0.029	0.070	0.436
Resin	0.025	−0.019	0.067	0.245
Step 2				
$\Delta R^2 = 0.003$, $p = 0.553$				
Total $R^2 = 0.147$, $p < 0.001$				
Constant	1.746	0.413	2.981	
Skunk	**0.096**	**0.051**	**0.143**	**<0.001**
Other grass	0.018	−0.030	0.069	0.477
Resin	0.025	−0.018	0.067	0.245
Age	−0.003	−0.046	0.050	0.905
Gender	−0.380	−1.064	0.317	0.268
Step 3				
$\Delta R^2 = 0.023$, $p = 0.005$				
Total $R^2 = 0.170$, $p < 0.001$				
Constant	0.913	−0.874	2.537	
Skunk	**0.146**	**0.018**	**0.278**	**0.024**
Other grass	0.014	−0.034	0.062	0.584
Resin	0.022	−0.021	0.064	0.298
Age	**0.078**	**0.012**	**0.156**	**0.037**
Gender	−1.030	−2.142	0.094	0.058
Age × skunk	**−0.006**	**−0.010**	**−0.002**	**0.003**
Gender × skunk	0.052	−0.019	0.121	0.160
Step 4				
$\Delta R^2 = -0.015$, $p = 0.138$				
Total $R^2 = 0.155$, $p < 0.001$				
Constant	−0.733	−2.865	0.922	
Skunk	**0.254**	**0.161**	**0.357**	**<0.001**
Age	**0.081**	**0.014**	**0.170**	**0.039**
Age × skunk	**−0.006**	**−0.010**	**−0.002**	**0.004**

CI, Confidence interval.

Significant predictor variables are shown in bold.

Days of skunk use, but not other grass or resin, predicted higher Severity of Dependence Scale scores. The relationship between skunk use and severity of dependence became stronger as age decreased.

Discussion

This study compared the profile of three cannabis types and their associations with cannabis dependence. Our findings clearly show that use of high-potency (skunk) but not low-potency (other grass, resin) cannabis is associated with an increased severity of dependence, especially in young people. Furthermore, the profile of high-potency (skunk) cannabis was marked in terms of negative effects (memory and paranoia) but also positive characteristics (preferred type and best high). It was also rated as the most available type, but was not the best value for money.

The past decade has seen a huge increase in the prevalence of high-potency (skunk-type) cannabis in England and Wales (King *et al.* 2004; Hardwick & King, 2008; Potter *et al.* 2008; Freeman *et al.* 2014) alongside rising demand for cannabis treatment in addiction services (NDTMS, 2014, 2015). Our findings are consistent with these observations, and are the first to our knowledge reporting a link between cannabis potency and severity of drug dependence. Thus, clinically, it might be useful (and desirable) to encourage skunk users at risk of/experiencing dependence to move to less potent forms of cannabis if they are not motivated to quit.

Younger people were especially vulnerable, displaying a stronger relationship between extent of skunk use and severity of dependence. This is in agreement with observations that more under 18's seek treatment for cannabis than all adults combined, unlike any other drug (NDTMS, 2014, 2015). Young people in our sample were also exposed to skunk from an earlier age; older adults tried resin first and had not tried skunk until an average of 2.42 years later. Given that these changes in the illicit market may have increased rates of cannabis dependence in the UK, it will be important to evaluate the impact of careful regulation of cannabis potency (e.g. as planned in Uruguay) and other legislative changes (e.g. in the US) on cannabis dependence.

One explanation for our findings is that greater THC exposure enhances the dependence-forming properties of cannabis. This interpretation is in keeping with preclinical research showing that THC is reinforcing in a dose-dependent manner (Tanda *et al.* 2000; Justinova *et al.* 2003). Titration by cannabis users appears to counteract higher THC concentrations, but only partially (Freeman *et al.* 2014; van der Pol *et al.* 2014). As a result, episodic use of high-potency cannabis will typically deliver larger doses of THC.

Interestingly, people in this study added less cannabis to their joints (based on the number of joints made out of 3.5 g) when using resin compared to other types. This may have further reduced their dose of THC, in addition to the low potency typical of resin. However, they took a similar number of days to smoke 3.5 g in total – perhaps suggesting that resin users smoke more joints with smaller amounts of cannabis (and possibly more tobacco), resulting in similar consumption of raw cannabis overall. The presence of CBD may also be relevant. Cannabis with a high ratio of CBD:THC (i.e. resin) reduced attentional bias to drug cues (a process implicated in addiction; Field & Cox, 2008) relative to low CBD:THC cannabis (i.e. skunk) (Morgan *et al.* 2010*b*). CBD was also found to reduce symptoms of

cannabis withdrawal in an open-label case study (Crippa *et al.* 2012).

Although our results support a relationship between cannabis potency and severity of dependence, they do not imply a causal relationship, and many other factors are likely to be involved. For example, a prospective study found no independent associations between indices of cannabis use (including preferred type and THC concentrations) and subsequent incidence of dependence (van der Pol *et al.* 2013). This study differed from ours in a number of respects, and included a number of additional predictors (e.g. socio-demographic, vulnerability and stress factors). Additionally, it used a between-subjects comparison of preferred cannabis type and potency as opposed to our within-subject analysis.

Contrary to our expectations, degree of cannabis use did not predict level of concerns about cannabis (memory, mental health, work or study, relationships, motivation, chronic lung disease, cancer, legal issues). This might reflect the varying susceptibility to cannabis-related harms between individuals. Another possible explanation is that more frequent users hold the belief that their use is not problematic. These findings also suggest that all levels of use can be associated with modest health concerns. This may imply that infrequent users who are not currently using treatment services are nevertheless worried about the effects of cannabis, and might benefit from help at an individual or population-based level.

It is also noteworthy that memory emerged as the strongest concern about cannabis use in this study, as this was also the most defining feature of high-potency cannabis. This is consistent with the high THC, low CBD profile of skunk. When acutely administered, THC produces robust and dose-dependent impairments in verbal memory (Curran *et al.* 2002; D'Souza *et al.* 2004) and these impairments can be ameliorated by co-administration of CBD (Morgan *et al.* 2010*a*; Englund *et al.* 2012). Similarly, skunk was identified as the type of cannabis most strongly associated with paranoia. This is consistent with evidence that the paranoia-inducing effects of THC can also be inhibited by CBD (Englund *et al.* 2012), and that regular skunk use is associated with an increased risk (Di Forti *et al.* 2009) and earlier onset (Di Forti *et al.* 2013) of psychosis, while resin/hashish is not, even in daily users (Di Forti *et al.* 2015).

Although skunk was most clearly defined by these negative effects, it was also rated as having the 'best high' and was considered the 'preferred type'. Clinical and public health interventions related to high-potency cannabis, focusing in its negative effects, should be interpreted in the context of users' own preferences. Given that skunk was rated as the most available type of cannabis, consistent with previous findings (Hardwick & King, 2008; Potter *et al.* 2008; Freeman *et al.* 2014) people who do prefer it will probably find it easy to obtain in the illicit market. On the other hand, those who do not prefer skunk – or find that its negative effects outweigh the desirable ones – may have little choice due to the current lack of available alternatives. Perhaps varieties of cannabis with weaker effects on memory and paranoia (e.g. other grass, resin) may be more desirable in this respect.

When comparing these lower potency varieties, it is somewhat surprising that resin was rated as having a better high and stronger effects on memory and paranoia, given that it generally contains lower THC and higher CBD than imported herbal cannabis (Hardwick & King, 2008). It may be relevant that variation in cannabinoid content is comparatively greater in resin (Potter *et al.* 2008) and some resin can be highly potent (e.g. 39.3% THC in the Netherlands; Pijlman *et al.* 2005). Such preparations are incredibly rare in the UK (Potter *et al.* 2008) but perhaps experience with especially potent forms of resin could have led some people to rate it as having the best high, and strongest effects on memory and paranoia.

This study has some limitations. First, it used a self-selecting (drug using) sample. This enabled a large number of cannabis users to be recruited, but it does limit the extent to which the findings can be attributed to the general population, or more problematic users, as dependence scores were modest on average. Second, because dependence was estimated using the SDS rather than a structured clinical interview, it was not possible to tease apart specific aspects of cannabis use disorder such as tolerance, withdrawal, craving, failing obligations, giving up other recreational interests, and persistent use in spite of problems. Additionally, the study was cross-sectional and causality cannot be established on the basis of these results. Indeed, it is quite plausible that reverse causation might explain our findings (e.g. as a result of dependence, people use more skunk). Third, skunk was used for more days per month than the other types, which might explain the reported association with dependence. However, variance in days per month of use was similar for each of the three types, suggesting that these data were equally appropriate to detect the existence of possible associations with dependence. Fourth, although we quantified use of three different cannabis preparations, we cannot be sure that the terms we used (e.g. skunk) were meaningful to the population tested (Potter & Chatwin, 2012), although similarly named types were predictive of actual THC and CBD concentrations elsewhere (Freeman *et al.* 2014).

Conclusion

Use of high-potency (skunk) cannabis is associated with an increased severity of dependence, especially

in young people. Skunk is also rated as having stronger effects on memory impairment and paranoia than other types of cannabis, but at the same time it produces the best high and is users' preferred type.

Acknowledgements

We thank all volunteers for taking part in the Global Drug Survey, Mixmag, *The Guardian*, and Ravi Das for their assistance, and Chandni Hindocha for her comments on an earlier version of this manuscript. We also thank two anonymous reviewers for their helpful comments and for suggesting additional analysis with age and gender. Preliminary data from this project were presented at the British Association for Psychopharmacology Summer Meeting, 2015. T. P. Freeman was supported by the Medical Research Council. Global Drug Survey is self-funded.

Declaration of Interest

A.W. is director and founder of Global Drugs Survey Ltd.

References

Coombes R (2014). Cannabis regulation: high time for change? *British Medical Journal* **348**, g3382.

Crippa J, Hallak J, Machado-de-Sousa J, Queiroz R, Bergamaschi M, Chagas M, Zuardi A (2012). Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report. *Journal of Clinical Pharmacy and Therapeutics*.

Curran VH, Brignell C, Fletcher S, Middleton P, Henry J (2002). Cognitive and subjective dose-response effects of acute oral Δ9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology* **164**, 61–70.

Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, Bianconi F, Gardner-Sood P, O'Connor J, Russo M (2015). Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry* **2**, 233–238.

Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, Handley R, Luzi S, Russo M, Paparelli A (2009). High-potency cannabis and the risk of psychosis. *British Journal of Psychiatry* **195**, 488–491.

Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, Stilo SA, Marconi A, La Cascia C, Marques TR, Pariante C (2013). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin* **40**, 1509–1517.

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu Y-T, Braley G, Gueorguieva R, Krystal JH (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* **29**, 1558–1572.

EMCDDA (2014). European Drug Report. European Monitoring Centre for Drugs and Drug Addiction.

Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, Stone JM, Reichenberg A, Brenneisen R, Holt D (2012). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *Journal of Psychopharmacology* **27**, 19–27.

Field M, Cox WM (2008). Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug and Alcohol Dependence* **97**, 1–20.

Freeman TP, Morgan CJ, Hindocha C, Schafer G, Das RK, Curran HV (2014). Just say 'know': how do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints? *Addiction* **109**, 1686–1694.

Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, Strang J (1995). The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction* **90**, 607–614.

Hardwick S, King LA (2008). *Home Office Cannabis Potency Study 2008*. Home Office Scientific Development Branch: UK.

Hindocha C, Freeman TP, Schafer G, Gardener C, Das RK, Morgan CJ, Curran HV (2015). Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. *European Neuropsychopharmacology* **25**, 325–334.

Home Office (2014). Drug Misuse: Findings from the 2013 to 2014 Crime Survey For England and Wales.

Justinova Z, Tanda G, Redhi GH, Goldberg SR (2003). Self-administration of Δ9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. *Psychopharmacology* **169**, 135–140.

King LA, Carpentier C, Griffiths P (2004). *EMCDDA INSIGHTS - An Overview of Cannabis Potency in Europe*. Office for Official Publications of the European Communities, Luxembourg.

Morgan C, Gardener C, Schafer G, Swan S, Demarchi C, Freeman T, Warrington P, Rupasinghe I, Ramoutar A, Tan N (2012). Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. *Psychological Medicine* **42**, 391–400.

Morgan CJ, Schafer G, Freeman TP, Curran HV (2010*a*). Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. *British Journal of Psychiatry* **197**, 285–290.

Morgan CJA, Curran HV (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *British Journal of Psychiatry* **192**, 306–307.

Morgan CJA, Freeman TP, Schafer GL, Curran HV (2010*b*). Cannabidiol attenuates the appetitive effects of [Delta] 9-Tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology* **35**, 1879–1885.

NDTMS (2014). *Adult Drug Statistics from the National Drug Treatment Monitoring System (NDTMS)*. Public Health England, London.

NDTMS (2015). *Young People's Statistics from the National Drug Treatment Monitoring System (NDTMS)*. Public Health England, London.

Pijlman F, Rigter S, Hoek J, Goldschmidt H, Niesink R (2005). Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. *Addiction Biology* **10**, 171–180.

Potter DJ (2014). A review of the cultivation and processing of cannabis (*Cannabis sativa* L.) for production of prescription medicines in the UK. *Drug Testing and Analysis* **6**, 31–38.

Potter DJ, Clark P, Brown MB (2008). Potency of Δ^9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *Journal of Forensic Sciences* **53**, 90–94.

Potter GR, Chatwin C (2012). The problem with 'skunk'. *Drugs and Alcohol Today* **12**, 232–240.

Russo EB (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology* **163**, 1344–1364.

Swift W, Copeland J, Hall W (1998). Choosing a diagnostic cut-off for cannabis dependence. *Addiction* **93**, 1681–1692.

Tanda G, Munzar P, Goldberg SR (2000). Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. *Nature neuroscience* **3**, 1073–1074.

UNODC (2014). World Drug Report. United Nations Office on Drugs and Crime.

van der Pol P, Liebregts N, Brunt T, Amsterdam J, Graaf R, Korf DJ, Brink W, Laar M (2014). Cross-sectional and prospective relation of cannabis potency, dosing and smoking behaviour with cannabis dependence: an ecological study. *Addiction* **109**, 1101–1109.

van der Pol P, Liebregts N, de Graaf R, Korf DJ, van den Brink W & van Laar M (2013). Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study. *Drug and Alcohol Dependence* **133**, 352–359.

Winstock AR, Mitcheson LR, Deluca P, Davey Z, Corazza O, Schifano F (2011). Mephedrone, new kid for the chop? *Addiction* **106**, 154–161.

Zuardi A, Shirakawa I, Finkelfarb E, Karniol I (1982). Action of cannabidiol on the anxiety and other effects produced by Δ9-THC in normal subjects. *Psychopharmacology* **76**, 245–250.

Medical Marijuana Consent Form

A qualified physician may not delegate the responsibility of obtaining written informed consent to another person. The qualified patient, or the patient's parent or legal guardian if the patient is a minor, must initial each section of this consent form to indicate that the physician explained the information and, along with the qualified physician, must sign and date the informed consent form.

This consent form contains three parts. Part A must be completed by all patients. Part B is only required for patients under the age of 18 with a diagnosed terminal condition who receive a certification for medical marijuana in a smokable form. Part C is the signature block and must be completed by all patients.

Part A: Must be completed for all medical marijuana patients

a. The Federal Government's classification of marijuana as a Schedule I controlled substance.

_____ The federal government has classified marijuana as a Schedule I controlled substance. Schedule I substances are defined, in part, as having (I) a high potential for abuse; (2) no currently accepted medical use in treatment in the United States; and (3) a lack of accepted safety for use under medical supervision. Federal law prohibits the manufacture, distribution and possession of marijuana even in states, such as Florida, which have modified their state laws to treat marijuana as a medicine.

_____ When in the possession of medical marijuana, the patient or the patient's caregiver must have his or her medical marijuana use registry identification card in his or her possession at all times.

b. The approval and oversight status of marijuana by the Food and Drug Administration.

_____ Marijuana has not been approved by the Food and Drug Administration for marketing as a drug. Therefore, the "manufacture" of marijuana for medical use is not subject to any federal standards, quality control, or other federal oversight. Marijuana may contain unknown quantities of active ingredients, which may vary in potency, impurities, contaminants, and substances in addition to THC, which is the primary psychoactive chemical component of marijuana.

c. The potential for addiction.

_____ Some studies suggest that the use of marijuana by individuals may lead to a tolerance to, dependence on, or addiction to marijuana. I understand that if I require increasingly higher doses to achieve the same benefit or if I think that I may be developing a dependency on marijuana, I should contact Dr. _____ (name of qualified physician).

d. The potential effect that marijuana may have on a patient's coordination, motor skills, and cognition, including a warning against operating heavy machinery, operating a motor vehicle, or engaging in activities that require a person to be alert or respond quickly.

_____ The use of marijuana can affect coordination, motor skills and cognition, i.e., the ability to think, judge and reason. Driving under the influence of cannabis can double the risk of vehicular accident, which escalates if alcohol is also influencing the driver. While using medical marijuana, I should not drive, operate heavy machinery or engage in any activities that require me to be alert and/or respond quickly and I should not participate in activities that may be dangerous to myself or others. I

understand that if I drive while under the influence of marijuana, I can be arrested for "driving under the influence."

e. The potential side effects of medical marijuana use.

_____ Potential side effects from the use of marijuana include, but are not limited to, the following: dizziness, anxiety, confusion, sedation, low blood pressure, impairment of short term memory, euphoria, difficulty in completing complex tasks, suppression of the body's immune system, may affect the production of sex hormones that lead to adverse effects, inability to concentrate, impaired motor skills, paranoia, psychotic symptoms, general apathy, depression and/or restlessness. Marijuana may exacerbate schizophrenia in persons predisposed to that disorder. In addition, the use of medical marijuana may cause me to talk or eat in excess, alter my perception of time and space and impair my judgment. Many medical authorities claim that use of medical marijuana, especially by persons younger than 25, can result in long-term problems with attention, memory, learning, drug abuse, and schizophrenia.

There is substantial evidence of a statistical association between long-term cannabis smoking and worsening respiratory symptoms and more frequent chronic bronchitis episodes. Smoking marijuana is associated with large airway inflammation, increased airway resistance, and lung hyperinflation. Smoking cannabis, much like smoking tobacco, can introduce levels of volatile chemicals and tar in the lungs that may raise concerns about the risk of cancer and lung disease.

_____ I understand that using marijuana while consuming alcohol is not recommended. Additional side effects may become present when using both alcohol and marijuana.

_____ I agree to contact Dr. _____ if I experience any of the side effects listed above, or if I become depressed or psychotic, have suicidal thoughts, or experience crying spells. I will also contact Dr. _____ if I experience respiratory problems, changes in my normal sleeping patterns, extreme fatigue, increased irritability, or begin to withdraw from my family and/or friends.

f. **The risks, benefits, and drug interactions of marijuana**.

_____ Signs of withdrawal can include: feelings of depression, sadness, irritability, insomnia, restlessness, agitation, loss of appetite, trouble concentrating, sleep disturbances and unusual tiredness.

_____ Symptoms of marijuana overdose include, but are not limited to, nausea, vomiting, hacking cough, disturbances in heart rhythms, numbness in the hands, feet, arms or legs, anxiety attacks and incapacitation. If I experience these symptoms, I agree to contact Dr. _____ immediately or go to the nearest emergency room.

_____ Numerous drugs are known to interact with marijuana and not all drug interactions are known. Some mixtures of medications can lead to serious and even fatal consequences.

I agree to follow the directions of Dr. _____ regarding the use of prescription and non-prescription medication. I will advise any other of my treating physician(s) of my use of medical marijuana.

_____ Marijuana may increase the risk of bleeding, low blood pressure, elevated blood sugar, liver enzymes, and other bodily systems when taken with herbs and supplements. I agree to contact Dr. _____ immediately or go to the nearest emergency room if these symptoms occur.

_____ I understand that medical marijuana may have serious risks and may cause low birthweight or other abnormalities in babies. I will advise Dr. _____ if I become pregnant, try to get pregnant, or will be breastfeeding.

g. The current state of research on the efficacy of marijuana to treat the qualifying conditions set forth in this section.

____ Cancer

- There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers, including glioma.

  There is evidence to suggest that cannabinoids (and the endocannabinoid system more generally) may play a role in the cancer regulation processes. Due to a lack of recent, high quality reviews, a research gap exists concerning the effectiveness of cannabis or cannabinoids in treating cancer in general.

- There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting.

  There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa.

____ Epilepsy

- There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for epilepsy.

  Recent systematic reviews were unable to identify any randomized controlled trials evaluating the efficacy of cannabinoids for the treatment of epilepsy. Currently available clinical data therefore consist solely of uncontrolled case series, which do not provide high-quality evidence of efficacy. Randomized trials of the efficacy of cannabidiol for different forms of epilepsy have been completed and await publication.

____ Glaucoma

- There is limited evidence that cannabinoids are an ineffective treatment for improving intraocular pressure associated with glaucoma.

  Lower intraocular pressure is a key target for glaucoma treatments. Nonrandomized studies in healthy volunteers and glaucoma patients have shown short-term reductions in intraocular pressure with oral, topical eye drops, and intravenous cannabinoids, suggesting the potential for therapeutic benefit. A good-quality systemic review identified a single small trial that found no effect of two cannabinoids, given as an oromucosal spray, on intraocular pressure. The quality of evidence for the finding of no effect is limited. However, to be effective, treatments targeting lower intraocular pressure must provide continual rather than transient reductions in intraocular

pressure. To date, those studies showing positive effects have shown only short-term benefit on intraocular pressure (hours), suggesting a limited potential for cannabinoids in the treatment of glaucoma.

____ Positive status for human immunodeficiency virus

- There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS.

  There does not appear to be good-quality primary literature that reported on cannabis or cannabinoids as effective treatments for AIDS wasting syndrome.

____ Acquired immune deficiency syndrome

- There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS.

  There does not appear to be good-quality primary literature that reported on cannabis or cannabinoids as effective treatments for AIDS wasting syndrome.

___ Post-traumatic stress disorder

- There is limited evidence (a single, small fair-quality trial) that nabilone is effective for improving symptoms of posttraumatic stress disorder

  A single, small crossover trial suggests potential benefit from the pharmaceutical cannabinoid nabilone. This limited evidence is most applicable to male veterans and contrasts with non-randomized studies showing limited evidence of a statistical association between cannabis use (plant derived forms) and increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder. There are other trials that are in the process of being conducted and if successfully completed, they will add substantially to the knowledge base.

____ Amyotrophic lateral sclerosis

- There is insufficient evidence that cannabinoids are an effective treatment for symptoms associated with amyotrophic lateral sclerosis.

  Two small studies investigated the effect of dronabinol on symptoms associated with ALS. Although there were no differences from placebo in either trial, the sample sizes were small, the duration of the studies was short, and the dose of dronabinol may have been too small to ascertain any activity. The effect of cannabis was not investigated.

____ Crohn's disease

- There is insufficient evidence to support or refute the conclusion that dronabinol is an effective treatment for the symptoms of irritable bowel syndrome.

  Some studies suggest that marijuana in the form of cannabidiol may be beneficial in the treatment of inflammatory bowel diseases, including Crohn's disease.

____ Parkinson's disease

- There is insufficient evidence that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson's disease or the levodopainduced dyskinesia.

Evidence suggests that the endocannabinoid system plays a meaningful role in certain neurodegenerative processes; thus, it may be useful to determine the efficacy of cannabinoids in treating the symptoms of neurodegenerative diseases. Small trials of oral cannabinoid preparations have demonstrated no benefit compared to a placebo in ameliorating the side effects of Parkinson's disease. A seven-patient trial of nabilone suggested that it improved the dyskinesia associated with levodopa therapy, but the sample size limits the interpretation of the data. An observational study demonstrated improved outcomes, but the lack of a control group and the small sample size are limitations.

____ Multiple sclerosis

- There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity.

Based on evidence from randomized controlled trials included in systematic reviews, an oral cannabis extract, nabiximols, and orally administered THC are probably effective for reducing patient-reported spasticity scores in patients with MS. The effect appears to be modest. These agents have not consistently demonstrated a benefit on clinician-measured spasticity indices.

____ Medical conditions of same kind or class as or comparable to the above qualifying medical conditions

- The qualifying physician has provided the patient or the patient's parent or legal guardian a summary of the current research on the efficacy of marijuana to treat the patient's medical condition.
- The summary is attached to this informed consent as Addendum_____.

____ Terminal conditions diagnosed by a physician other than the qualified physician issuing the physician certification

- The qualifying physician has provided the patient or the patient's caregiver a summary of the current research on the efficacy of marijuana to treat the patient's terminal condition.
- The summary is attached to this informed consent as Addendum_____.

____ Chronic nonmalignant pain

- There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

The majority of studies on pain evaluated nabiximols outside the United States. Only a handful of studies have evaluated the use of cannabis in the United
States. and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse. In contrast, many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States. Pain patients also use topical forms.

While the use of cannabis for the treatment of pain is supported by well controlled clinical trials, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States.

h. That the patient's de-identified health information contained in the physician certification and medical marijuana use registry may be used for research purposes.

_____ The Department of Health submits a data set to the Consortium for Medical Marijuana Clinical Outcomes Research for each patient registered in the medical marijuana use registry that includes the patient's qualifying medical condition and the daily dose amount and forms of marijuana certified for the patient.

PART B: Certification for medical marijuana in a smokable form for a patient under 18 with a diagnosed terminal condition.

___ Initial here if you are not a patient under 18 with a diagnosed terminal condition who will be receiving medical marijuana in a smokable form. After initialing here, complete part C.

If the patient is under 18, has a diagnosed terminal condition, and will be receiving medical marijuana in a smokable form, please review and initial the remainder of Part B before completing Part C.

Respiratory Health

____ Exposures to tobacco smoke and household air pollution consistently ranks among the top risk factors not only for respiratory disease burden but also for the global burden of disease. Given the known relations ships between tobacco smoking and multiple respiratory conditions, one could hypothesize that long-term cannabis smoking leads to similar deleterious effects of respiratory health, and some investigators ague that cannabis smoking may be even more harmful that of tobacco smoking. Data collected from 15 volunteers suggest that smoking one cannabis joint can lead to four times the exposure to carbon monoxide and three to five times more tar deposition than smoking a single cigarette.

Cognitive and Psychosocial Development

____ Researchers are still studying the long-term health effects of marijuana. Most people agree that marijuana use hurts adolescents more than adults. It is during the period of adolescence and young adulthood that the neural substrates that underlie the development of cognition are most active. Adolescence marks one of the most impressive stretches of neural and behavioral change with substantial a protracted development in terms of both brain structure and function. As a result, cannabis and other substance use during this period may incur relatively greater interference in neural, social, and academic functioning compared to late developmental periods.

- There is moderate evidence of a statistical association between acute cannabis use and impairment in the cognitive domains of learning, memory, and attention.
- There is limited evidence of a statistical association between sustain abstinence form cannabis use and impairments in the cognitive domains of learning, memory, and attention.
- There is limited evidence of a statistical association between cannabis use and impaired academic achievement and education outcomes.

- There is limited evidence of a statistical association between cannabis use and increased rates of unemployment and/or low income.

- There is limited evidence of a statistical association between cannabis use and impaired social functioning or engagement in developmentally appropriate social roles.

____ Addiction

Marijuana, like some other brain-altering substances, can be addictive. Nearly one in 10 marijuana users will become addicted. Starting to use marijuana at a younger age can lead to a greater risk of developing a substance use disorder later in life. Adolescents who begin using marijuana before age 18 are four to seven times more likely than adults to develop a marijuana use disorder

Part C: Must be completed for all medical marijuana patients

_____ I have had the opportunity to discuss these matters with the physician and to ask questions regarding anything I may not understand or that I believe needed to be clarified. I acknowledge that Dr. _____ has informed me of the nature of a recommended treatment, including but not limited to, any recommendation regarding medical marijuana.

Dr. _____also informed me of the risks, complications, and expected benefits of any recommended treatment, including its likelihood of success and failure. I acknowledge that Dr. _____informed me of any alternatives to the recommended treatment, including the alternative of no treatment, and the risks and benefits. Dr. _____ has explained the information in this consent form about the medical use of marijuana.

Patient (print name) _____

Patient signature or signature of the parent or legal guardian if the patient is a minor:

_____ Date _____

I have explained the information in this consent form about the medical use of marijuana to _____ (Print patient name).

Qualified physician signature:

_____ Date _____

Witness:

_____ Date_____

6488-9.018, F.A.C.
64815-14.013, F.A.C.
DH-MQA-5026 (Rev. 04/19)