THE JOURNAL OF
GLOBAL DRUG POLICY AND PRACTICE

20 Flaws in Study Finding No Health Problems in Adult Males Who Were Chronic Marijuana Users as Teens, Young Adults

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A new study has caused quite a stir among would-be marijuana cognoscenti because it contradicts major research about the impact of marijuana on physical and mental health. The neuroscientist, Bertha K. Madras of Harvard Medical School looked briefly at the study. Dr. Madras served as Deputy Director for Demand Reduction in the White House Office of National Drug Control Policy from 2006 to 2008 . . . She writes:

A recent manuscript by Bechtold et al[1], describes a longitudinal assessment of a population of marijuana users which, after data collection, were divided into four user groups: (1) non-users to low use (48%, n=186); (2) limited to adolescent use (10%, n=38); (3) late initiators and increasing (20%, n=76); (4) early onset with chronic use (22%, n=86). Marijuana use was monitored from adolescence (age 15) into young adulthood (age 26). Ten years later, *and ten years after the last determination of marijuana use,* study authors asked the subjects, now at an average age of 35.8 years, to report their health status. Each of the four groups self-reported no differences in physical or mental health problems in their mid-thirties. The authors concluded that regardless of how much and how long marijuana was used, and regardless of race, the physical and mental health problems of these four groups were similar. That is, high marijuana use for prolonged periods was not associated with any physical or mental health problems. They

also claimed that this is a definitive study because it was longitudinal and superior to other published reports on long term health consequences of marijuana.

A critical evaluation of the validity of the findings and sweeping conclusions is essential, lest they are interpreted inappropriately. A perusal of the study and the authors' stated caveats in the manuscript reveal significant weaknesses, with the use of an unrepresentative, possible archaic population, inadequate sample size, inadequate methodologies to assess mental health and physical problems, (self-reports, evaluation of psychiatric status without considering the "spectrum" nature of psychiatric conditions, and absence of addiction evaluation). The findings conflict with other well designed longitudinal studies that assess long term consequences of marijuana use with early age of initiation of marijuana.

This type of study would not approach or fulfill rigorous criteria for longitudinal research, as exemplified by the 2014 NIDA funding opportunity with similar goals (*see Appendix*). The conclusions conceivably are compromised by the following perceived shortcomings of the study.

Population Concerns

1. **The sample size, 386 people, was too small to detect a marijuana effect on psychotic disorders or on other health conditions.** NIDA recommends a sample size of 10,000 to detect differences *(see Appendix).* About 50% of the subjects – age 14 - were selected on the basis of their high scores on anti-social behaviors (conduct problems) and the remainder from adolescents without high anti-social behavior scores, but it is not clear whether the drop-out rate from the study was equally represented by both categories. Did more people

with early onset anti-social behaviors drop out and does this skew the conclusions? Was there under-sampling of a population at highest risk? There is strong and accumulating evidence that marijuana use is associated with psychosis, with earlier age of onset of schizophrenia, and with worsening of psychotic/schizophrenic symptoms. These association studies were gleaned from thousands of people, not from fewer than 400 subjects, especially when only 86 people are in the high risk group. The small sample size would also make it difficult to detect other serious marijuana-associated medical problems. Reporting of cardiovascular complications related to marijuana and the extreme seriousness of these events (death rate of 25.6%) is increasing, but this occurs in a small number of users (one estimate is 1.8%). Marijuana is a possible risk factor for cardiovascular disease in young adults[6], with a temporal association between marijuana use and heart attacks, sudden cardiac death, and for stroke, transient ischemic attack, and marijuana-induced arteritis.[7] Pulmonary symptoms attributable to marijuana use, even with less intense use, include chronic bronchitis, daily cough, phlegm production (four quality studies document these findings). No power analysis indicates adequacy of sample size.

Think about this: The prevalence of schizophrenia is 1 in 100. If you sample only 86 subjects of the riskiest group, "early onset chronic users" category, it is unlikely that you can detect a significant increase in prevalence of psychosis or schizophrenia. Another example: a recent study found the incidence of serious cardiac effects of marijuana in 1.8% of heavy users. Was the sample of early onset chronic users (86 people) large enough to detect serous cardiac effects, especially from self-reports?

2. **The study does not have a drug-naïve population for comparative measures of outcomes.** They report that the amount of marijuana used during adolescence and early adulthood had no effect on the occurrence of a range of health problems**.**

   Think about this: The study has no group that controls for a general, representative population, a non-drug using population. Some other studies have shown different outcomes among youth or young adults who choose not to use, those who use occasionally, or among heavy users. What populations are these groups compared to? Are the group sizes large enough to detect differences?

3. **The populations and use patterns investigated in this study are anachronistic and conceivably irrelevant for 2015.** Subjects were initially screened in 1987-1988, with a majority of users recruited that did not fall into the heavy use range (daily or near daily use), a use pattern increasingly observed at the present time. The majority of subjects used marijuana during the 1990's when the psychoactive THC content of marijuana was relatively low compared with current concentrations.

   Think about this: The most serious health outcomes associated with marijuana use, including addiction, occur in heavy users (daily or near daily use) using for long periods of time. Currently, marijuana access has risen rapidly as its legal status changes; its perception of harm has plummeted among youth, along with a rising perception that as a medicine it is safe and can be used daily. Daily use of high potency marijuana among adolescents and young adults is near or at its highest level in nearly three decades. The populations of this

study may be irrelevant to current trends, especially since 2009, as marijuana potency is at its highest level ever; availability is greater because of reduced federal and state oversight, as daily use increases, and perception of harm declines. These factors conceivably influence self-reporting of effects and their magnitude. Are the outcomes of this study relevant to current use patterns and marijuana potency?

4. **The population is not representative of the general population: (a) the prevalence of concussions (27.7%) is inordinately high. (b) death by gunfire is inordinately high.** No explanations are offered for the abnormally high prevalence of concussions or death by gunfire, and whether this population has a higher than average prevalence of cognitive impairment. Was there a relationship between concussions and marijuana use or self-reporting of adverse health problems?

   Think about this: The overall rate of traumatic brain injury (concussions) presenting in emergency departments in the United States (recent CDC statistics) is 19 per 100,000 persons; for males in this age group, it is about 470 per 100,000 persons (or 4.7 for each 1,000 persons). A concussion rate of 27% of this population (270 per 1000 persons) is about 60 times higher than the general population within this age range. Some research studies with rigorous criteria exclude subjects with traumatic brain injury because of the potential for cognitive impairment. The high numbers of concussions and deaths due to gunfire are anomalous if compared to statistics within the general population. Is this sample representative?

5. **Self-reported medical health problems by these subjects differ from population statistics, on the basis of occurrence by race.** According to CDC statistics in 2010, the prevalence of diseases in the general population among African American (AA) adults compared to white (W) adults is different than reported in this study. The CDC ratios (AA:W) for the general population are: Diabetes, CDC = 1.6:1; this study = 4:0. Chronic kidney disease, CDC = 1.14:1, this study = 0:0.6. Sexually transmitted diseases, CDC = 4:1; this study = 0.5:1.1.

   Think about this: The health problems self-reported by the African-Americans and white subjects may or may not be accurate, but they differ from the CDC prevalence data for the general population. Differences highlight the need for recruiting sufficiently large numbers of subjects to be representative of the population as a whole. Do differences reflect the unusual populations of this study, which may not generalize to the entire population?

Methodological Concerns: Outcome Measures

6. **The purpose of the study was to determine whether different patterns of marijuana use among youth affected mental and physical health differently. All findings are based on self-reports, an inadequate method for measuring outcomes – self reports, because of potential bias, recall errors, and reliance on self-knowledge of medical conditions.** The authors did not investigate medical records, did not confirm marijuana and other drug use with biometric tests, did not interrogate contacts, and did not inquire about sequence of use of other drugs.

***Think about this*:** More than 75% of people harboring a substance use disorder (SUD), based on objective DSM-IV criteria (Diagnostic and Statistical Manual-IV), do not think they have a SUD and do not seek treatment[2]. To rely solely on self-reporting of mental or physical health problems with a questionnaire, raises doubts about the overall study design and conclusions. Other examples: Fifty percent of men who die of heart disease had no obvious symptoms. A diagnosis of diabetes or high blood pressure is made by biometric testing, not by self-reports. Without confirmation from medical records or physician-initiated tests, is it possible to be self-aware of high blood pressure or diabetes with certainty?

7. **Following from #6 above, there is no evidence that subjects reported health outcomes based on their medical records. Authors did not report whether study participants had visited a physician during the past year, past five years or ten years since the last contact. Confirmation of medical conditions by a medical record would strengthen the conclusions.** The core outcomes of this study are mental and physical health. Knowing whether the mental and physical health of subjects in this study had been objectively diagnosed by a physician or specialist (psychiatrist, addiction medicine) is critical. The unknown medical record, combined with an assumption that subjects' self-reports were accurate, diminish the convictions of the authors' conclusions.

Think about this: Many health problems are not apparent to individuals until they are measured by a healthcare professional; addiction, high blood pressure, diabetes, cancer, cognitive impairment. Were all subjects reporting results from a recent annual checkup?

Unless this information and results are provided, can one assume that self-reports are accurate?

8. **Following from #6, #7 above, mental health diagnoses were based on questionnaires, not on biometric testing or long term assessment (mental health diagnosis requires more than a single session and evaluation over the span of months).** The diagnosis of psychosis, mood disorders, anxiety disorders, may rely solely on a person's response to a single oral or written questionnaire or impressions of their own health, but a definitive diagnosis for a serious mental health problem, such as schizophrenia, requires systematic questioning and over a significant period of time to determine whether symptoms persist and are not temporary aberrations. Moreover, mental health problems including substance use disorders (addiction) occur along a continuum of mild to severe. It is possible that the focus on a diagnosis of a psychotic disorder in the current study limited their ability to detect subtle effects of marijuana use on brain function, thought processes or early psychotic symptoms. Scores were not generated that reflect this continuum. Authors arbitrarily selected a cut-off point to rate the presence or absence of a diagnosis.

***Think about this**:* It is simple to detect one's own asthma or headache but, for many mental health problems, self-diagnosis may be inaccurate. Can one know if they are developing subtle signs of a mental problem or cognitive impairment unless measured objectively? Can one know if an early stage of cancer is present unless discovered by imaging, by biopsy, or gene expression profiling? Can one know if asymptomatic heart disease is present without ECG testing? Is self-diagnosis of an early stage of mental illness reliable?

Were subjects reporting their personal self-assessment or were they reporting results from a physician's medical and psychiatric examination?

Methodological Concerns: Marijuana Use

9. **The investigators divided marijuana users over time into four groups, using model fit statistics. The chart showing marijuana use over time for these four groups provides no error bars indicating whether these groups are significantly different or overlap at each age during the study.**

   Think about this: One would assume the groups were different, based on the four-group solution that was selected on the basis of model fit statistics, substantive interpretation, face validity of classes, parsimony, and consistency of findings with prior research. But, it would be helpful if error bars representing range of use at each age were included to assure the reader that the group divisions based on subjective criteria (interpretation, face validity of classes, parsimony, and consistency of findings with prior research) are transparently clear at each age.

10. **Some data of the marijuana use component are missing: 46% of the subjects had voids in data.** Almost half of the subjects did not report marijuana use at various times during the 10 years of survey. This partial set of data is problematic, even though authors claim missing data was similar to those who yielded full data sets and it is possible to interpolate missing data. Reasons for these data gaps should be provided.

    Think about this*:* If a segment of data are not available, does it invalidate or skew the chart showing trends of the four groups?

11. **Marijuana use was not questioned at the end of the study (age 36 years).** Strong longitudinal studies have shown that early onset and continued heavy use of marijuana is associated with or may be a causative agent in long term adverse effects on educational achievement, employment, welfare dependency, use of other illicit drugs, psychotic symptoms, I.Q. reduction, others [3-5]. This study provides marijuana use rates until age 26, measures life outcomes at age 36 but doesn't ask subjects whether they used marijuana from age 26-36 until age 36, and if so, frequency and amount. Most users apparently were not consuming daily or nearly daily until age 26, and three of the four groups had largely stopped using by the age of 26. Why was marijuana use not measured at the end of the study?

    ***Think about this**:* It is critical to know whether the people using marijuana from age 15-26 years, were still using at age 36, at which age health outcomes were questioned. If you are studying whether marijuana has interfered with the mental and physical health of subjects at the present time, it is not logical to interrogate whether they are currently using, or if they stopped and when they stopped? If they stopped 10 years before the study, then long term consequences may be less likely.

12. **Marijuana potency was far lower** (1980's to 1990's) during the period of marijuana consumption of this population. This conceivably affects outcomes and consequences.

13. **Quantity, frequency, potency of marijuana use is a critical measure. Frequency and potency were not questioned.** The main outcome measure was the number of times

marijuana was used during the year. The patterns of use, number of times used each day, potency, were not interrogated during each annual survey. This void makes it difficult to compare with other studies.

Methodological Concerns: Outcomes Not Measured

14. **Marijuana addiction (cannabis use disorder or CUD), among the most significant of the adverse effects of marijuana was not interrogated.** The prevalence of CUD is related to age of onset, quantity and frequency of use and closely linked to other life outcomes.

***Think about this*:** Addiction is among the most prominent effects of chronic marijuana use, and yet the study did not ask about addiction.

15. **Life outcomes were not measured (employment, educational achievement) at the end of the study.** Other strong longitudinal studies have interrogated life outcomes and concluded that marijuana has adverse long term effects on employment and educational achievements, other social consequences, as a function of age of onset and quantity used[3-5].

***Think about this**:* Longitudinal studies indicate that heavy continuous marijuana use is associated with lower socioeconomic status and achievements (e.g. college education, employment) than infrequent or no use. When an individual is using marijuana very frequently for a number of years, are they more or less likely to maintain a job, complete high school or college education, be on welfare?

16. **Cognitive testing was not measured.** Cognitive impairment is one of the hallmarks of acute and possibly long term marijuana use. It is also associated with other adverse life outcomes.

    Think about this: If you were designing a study to learn whether an intoxicant, known to interfere with learning, memory, executive function, affects your mental and physical health, would you omit evaluating learning and memory and other types of brain function, from the study?

17. **A number of health problems questioned (e.g. cancer, high blood pressure, heart attacks, strokes) arise later than the average age of the subjects (mid-30's).** The health questionnaire was filled out by marijuana users in their mid-30's, an age at which most significant health problems are not yet manifest.

18. **Acute effects of marijuana were not asked: intoxication, accidents, emergency department mentions, unplanned pregnancies, HIV-AIDS.** For example, a recent European study collected Emergency Department data from 14 European centers for six months to determine acute toxicity of marijuana. Of the sample, 356 (16.2 %) involved marijuana alone or together with other drugs/alcohol and 1.6 % with marijuana alone. Of the 35 non-fatal lone marijuana presentations, the most commonly reported features were agitation/aggression (22.9 %), psychosis (20.0 %), anxiety (20.0 %) and vomiting (17.1 %). There was one fatality due to prolonged cardiac arrest, with no other drugs detected.[6]

Think about this: Acute marijuana toxicity can lead to emergencies requiring medical attention. Does omission of this from the questionnaire achieve a comprehensive view of medical consequences of marijuana?

Citations and Comparison with Other Studies

19. **Authors omit mention of important recent longitudinal studies that show different outcomes than their own study.** Other carefully controlled and longitudinal studies have shown that early age of onset of marijuana use is associated with a number of mental and physical consequences, including addiction, cognitive deficits, mental health problems, educational, employment outcomes and others. Citations 3 and 4 are not mentioned, others are dismissed with a list of weaknesses, even though the current study is fraught with significant weaknesses.

20. **The authors attempt to support their conclusions by dismissing well designed reports by others.** In the introduction, they do not discuss severe limitations of their own study: (e.g. daily use of high potency marijuana is currently at its highest level in 30 years of surveys, in contrast with their subjects' marijuana use over 10-20 years ago; weaknesses of self-reported medical and psychiatric conditions, and others as stated above). Instead, the introduction curiously offers a critique, entitled ***Limitations in Prior Research.*** In it they conclude that "prior research has produced mixed findings regarding the associations between chronic marijuana use and indicators of physical and mental health, …and that individuals who begin using marijuana frequently during early adolescence and those who use at high frequencies throughout adolescence and young adulthood tend to develop more

health problems (i.e., psychotic symptoms, respiratory problems) than infrequent/nonusers, *in contradistinction to their own findings.*

Think about this: In their own critique of reports by others, they state that early onset, frequent marijuana users tend to develop more health problems than infrequent users, but there is no effort to reconcile their negative findings with positive findings of others.

(1) They claim this study is among a "handful of studies that have been able to prospectively delineate subgroups of individuals with varying developmental patterns of marijuana use from adolescence into young adulthood". The strength of the present study was to document marijuana use, but not in depth and not confirmed by biometric testing, annually for the decade of life encompassing adolescence and early adulthood. Yet, other research has interrogated key variables, age of onset, frequency and quantity of marijuana use (confirmed with biometric testing), some in prospective, longitudinal studies, others in cross-sectional studies. The medical record at the study's inception is of limited value because it is neither comprehensive nor independently verified. The initial assessment of 15 year old boys was inadequate and was not followed by a longitudinal assessment, except for marijuana use. The 10 year hiatus in collection of marijuana use data is a weakness. Self-reports of mental and physical health are inappropriate.

(2) They claim that "few longitudinal studies have examined whether young men who exhibit early and chronic developmental patterns of marijuana use are more likely to exhibit both physical and mental health problems in their mid-30s". Unfortunately, this

study does not answer this question because of the quality of the outcome measures, no marijuana use patterns recorded for 10 years, and the only medical and mental health outcomes are reported by mothers of the subjects around age 15, and by the subjects themselves at ~ age 36.

(3) They claim that "Many studies have failed to control for important confounding factors, such as health problems that predated the onset of regular marijuana use and co-occurring use of tobacco, alcohol, and hard drugs". Yet, they did not interrogate documented and age-appropriate deficits associated with marijuana use, at the onset of the study-in-depth psychiatric status, cognitive impairment, declining academic performance, school drop-out rates, accidents, and others, were not interrogated in this survey.

Limited References

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Appendix

An Example of a Well-Designed Longitudinal Study

NIDA Funding Opportunity: *http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-15-015.html*

Research Design and sample should describe the following:

- **A longitudinal single-cohort design to prospectively examine the neurodevelopmental and behavioral effects of substance use from early adolescence through the period of risk for substance use and substance use disorders**.
- **Participants, approximately ages 9-10 at baseline**, who are largely naïve to substance use at the time of study enrollment; the focus on a largely asymptomatic population at baseline provides the opportunity to define brain and behavioral risk factors and trajectories before the onset of substance use;
- **A design with a sample size that is sufficiently large to achieve the study goals;** preliminary estimates indicate **a sample size of approximately 10,000 participants**

(combined across sites) at the end of the 5-year funding cycle would be needed, **though a smaller sample can be proposed if justified by feasibility and statistical-power analyses;**

- **A sampling strategy designed to establish a community-based sample that is broadly representative of and generalizable to the U.S. general population as a whole,** including males and females, as well as major racial, ethnic, and sociodemographic subgroups of the population; it is recognized that the level of precision achieved for various subgroups may vary, and that probability-based sampling and oversampling of certain demographic subgroups or geographical regions may be required;
- **A sampling design that considers *oversampling* of population subgroups at greater risk for uptake of substance use during adolescence (e.g., positive family history of substance use disorders, externalizing psychopathology, disinhibitory traits, prenatal exposure to substances**);
- **A research approach that considers incorporating genetically informative designs** (e.g., family based) or subjects (e.g., twins, siblings);
- **A sampling design to produce geographical variation of macro-level factors associated with substance use** (e.g., state-level policies concerning the permissiveness of marijuana, alcohol, and tobacco use; regional variation in prevalence of marijuana, alcohol, and tobacco use; rural, urban and suburban populations);
- **State-of-the-art data-collection procedures (e.g., computer-administered/assisted interviews), practices (e.g., cultural matching) and quality-control processes (e.g., random verification, logic-checking);**

- **Standardized measures that, where possible, are compatible with data-harmonization efforts** (e.g., PhenX Toolkit) and ongoing studies of substance use and neurodevelopment;
- **Comprehensive multi-informant (**e.g., respondent, parent/guardian, sibling, etc. as appropriate) assessment of substance use to permit estimates of prevalence, incidence, and change in use patterns (e.g., quantity, frequency) by specific substances (e.g., nicotine, alcohol, marijuana), products and product types (cigarettes, e-cigarettes, snuff, beer, liquor, joints, blunts), and modes of administration (e.g., inhalation, oral, drinking, nasal)**;** measures of change should be sensitive enough to detect dynamic patterns among adolescents as they enter and pass through the period of risk for substance use;

Behavioral Measures and Biospecimens should describe the following:

- **Comprehensive and multi-level assessment of predictors, mediators, moderators, and outcomes associated with substance use** (e.g., demographics, pubertal status, personality traits, parental monitoring, peer group deviance, family structure, parent-child relationships, prosocial behaviors, romantic relationships, stressful events, availability of substances, state and local policies related to marijuana, alcohol, and tobacco use, educational attainment, learning disability designation or receipt of services, crime, unemployment, experience and/or witnessing of trauma or violence);
- **Assessment of concurrent and historical participation in interventions that may prevent or mitigate substance use and its consequences** (e.g., pre- and post-natal prevention programs; Head Start; receipt of counseling, psychotherapy and other

behavioral health interventions or services; family or classroom-based prevention interventions);

- **Comprehensive measurement of confounders and other risk factors** (e.g., prenatal exposure, abuse or trauma, drug availability, exposure to environmental risk factors, sport injuries especially to the head, etc.);
- **Rigorous quantitative and categorical assessment of symptomatology and psychiatric disorders, including severity;**
- **Family history assessment of substance use disorders and other psychopathology**;
- **Age-appropriate assessment of HIV-risk knowledge and behaviors**;
- **Neuropsychological battery of tests that is developmentally sensitive and that allows for the assessment of major neurobehavioral dimensions associated with substance use** (e.g., attention, information processing, learning and memory, cognitive control, motivation, emotional regulation, disinhibition, risk taking);
- **Screening for drug intoxication prior to behavioral, cognitive, or functional imaging sessions and neuropsychological assessment, with delineated thresholds for inclusion/exclusion**;
- **Clear and justified inclusion/exclusion criteria to identify individuals unable to complete the assessment protocol for various reasons** (e.g., use of certain prescribed medications, language/reading impairments, **brain injury**, severe mental illness, etc.);
- **Detailed plans and procedures to collect, process, analyze, and store biospecimens (e.g., urine, blood, saliva, hair) indicative of substance exposure;**

- **Additional biospecimens should be collected for subsequent research on genetic/epigenetic factors influencing or affected by substance use, with accompanying plans for analyses.**

About the Author

Dr. Bertha K. Madras is Professor of Psychobiology, Department of Psychiatry at Harvard Medical School (HMS), and is cross-appointed at the Massachusetts General Hospital. She served as Deputy Director for Demand Reduction (prevention, intervention, treatment) in the White House Office of National Drug Control Policy (ONDCP), a Presidential appointment confirmed unanimously by the US Senate. At Harvard, her multidisciplinary research focuses on neuropsychiatric diseases and addiction biology, documented in over 150 manuscripts and as co-editor of books "The Cell Biology of Addiction", "Effects of Drugs in the Human Nervous System", "Imaging of the Human Brain in Health and Disease". At ONDCP, she incorporated Screening, Brief Intervention, Referral to Treatment (SBIRT) into the national drug control strategy, spearheaded SBIRT CPT®, other billing code approvals, Medicaid reimbursement, SBIRT adoption by Health Resources and Services Administration, the Veterans Administration, recruitment of Federal healthcare insurers, a UN declaration of endorsement, and other initiatives. In service to the public, she directed creation of a Museum exhibit, a CD (licensed by Disney Corp), "Changing your mind: drugs in the brain" for the Boston Museum of Science. She has given hundreds of presentations worldwide, on how drugs affect the brain and consults to government, organizations and industry. She holds 19 patents, is a recipient of a NIDA Public Service award, a NIH MERIT award, American Academy Addiction Psychiatry Founders' Award, and Marian Fischman Award. A brain imaging agent strategy she developed was cited

by The Better World Report, 2006, as one of "25 technology transfer innovations that changed the world". Her experiences in translational neurobiology, government and public service afford her a unique perspective on science and public policy.

Conflict of Interest

I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled: *"20 Flaws in Study Finding No Health Problems in Adult Males Who Were Chronic Marijuana Users as Teens, Young Adults."*