faith SEEKING UNDERSTANDING

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Marijuana Research Findings

There seems to be a growing consensus on the medical and mental health concerns associated with smoking marijuana. Beginning in the summer of 2007, a series of research studies into the health risks of smoking marijuana started to appear in medical and research journals. Several of them are summarized here for your convenience. I will periodically update this synopsis of research as new studies on marijuana are made public. Most of the following studies should be available online if you want more information. This article was last updated in December of 2019.

The 2019 World Drug Report estimated that 188 million people used cannabis in 2017, equivalent to 3.8% per cent of the global population between the ages of 15 and 64. Since 1998, global cannabis use has increased by about 27%, reflecting the growth in the global population between 1998 and 2014. Since 2009, cannabis consumption had been increasing in the Americas.

As of the 2019 election, there are now ten states where recreational marijuana is legal, and 34 states where medical marijuana is legal and six states where CBD oil is legal. In 2016 24 million Americans aged 12 and over were estimated to have used marijuana in the past month. This corresponds to about 8.9% of the population 12 and over. Marijuana in early adolescence, when developing brains are susceptible to environmental influences, is a particular concern. In 2016, 6.5% of U.S. youths between the ages of 12 and 17 reported using marijuana within the past month; and 20.8% of the individuals between the ages of 18 and 25 (2.8 times the rate of 12 to 17-year olds) had used marijuana at least once in the past month.

Adverse Health Effects from Marijuana Use

Nora Volkow and three others published a review article, "Adverse Health Effects of Marijuana Use," in the June 5, 2014 issue of *The New England Medical Journal*. They summarized the current state of the scientific findings on the adverse health effects related to the recreational use of marijuana.

Their review focused on the areas where the evidence was the strongest. In a table summarizing their confidence in the evidence for adverse effects of marijuana on health and well-being, they gave the following assessment of marijuana use, particularly with heavy or long-term use that starts in adolescence. They summarized the results of their review of the literature on adverse effect from marijuana use as follows:

> Marijuana, like other drugs of abuse, can result in addiction. During intoxication, marijuana can interfere with cognitive functions (e.g. memory and perception of time) and motor function (e.g. coordination), and these effects can have detrimental consequences (e.g. motor-vehicle accidents). Repeated marijuana use during adolescence may result in long-lasting changes in brain function that can jeopardize educational, professional, and social achievements. . . . . As policy shifts toward legalization of marijuana, it is reasonable and probably prudent to hypothesize that its use will increase and that, by extension, so will the number of persons for whom there will be negative health consequences.

Their article is a good summary of the research in several of the following areas. The article provides data with a high level of confidence on the adverse effects of addiction, diminished lifetime achievement, motor vehicle accidents, and symptoms of bronchitis. They had a medium level of confidence in the data on abnormal brain development, the progressive use of other drugs, schizophrenia, and depression and anxiety. Also see my blog article, "Marijuana & Its Adverse Health Effects."

A German review study by Hoch et al., "Risk Associated with the Non-Medical Use of Cannabis," sought to summarize the current state of knowledge regarding the physical and mental adverse effects of intensive recreational cannabis use. They seem to have come to conclusions similar to the Volkow et al. study. Hoch et al. noted the potential for addiction and withdrawal, mild negative effects on learning capacity, neurocognitive impairments with adolescents, an increased risk of psychosis, and others. "Further research is required to clarify the causal nature of the links between cannabis consumption patterns and adverse events."

> Empirical data have now clearly shown that starting early in life and regularly using high amounts of cannabis for a long period of time increases the risk of various mental and physical disorders and endangers age-appropriate development. Because many studies have failed to control properly for confounding variables, it still cannot be stated beyond doubt that there is a causal connection between cannabis consumption patterns and cognitive damage or the development of comorbid psychic or somatic disorders. The worldwide increase in the THC content of cannabis may increase the health risks, particularly for adolescent users. Further research is required to determine why some people are more affected than others by the unfavorable consequences.

Another long-term study of chronic marijuana use among young adult men by Bechtold et al., was published in the journal, *Psychology of Addictive Behavior*. The study used data from The Pittsburgh Youth Study, a longitudinal study that followed seventh grade students until they were 36. The study found that chronic marijuana users were no more likely than other groups to experience several physical or mental health problems, including early onset psychosis and heart problems. Some limitations in applying the findings of this study would include the fact that participants were only followed until the age of 36, perhaps too early for many of the health problems to become evident. Another difference was that the heaviest use category for marijuana was "more than 3 times per

week," while Volkow et al. seems to have been looking at daily or almost daily use. See the Bechtol et al. article at: http://www.apa.org/pubs/journals/releases/adb-adb0000103.pdf

Cannabinoid Hyperemesis Syndrome (CHS)

There is a curious new disorder related to heavy marijuana use called cannabinoid hyperemesis syndrome (CHS). *High Times* described CHS as a rare form of cannabinoid toxicity that developed in chronic smokers. The author suggested this meant smoking three to five times daily for several years. "This should not, by any means, hurt marijuana's reputation for being the safest recreational drug around, but people need to be aware of the syndrome's existence. If you know anyone with these symptoms tell him or her go to a doctor and stop smoking." Remember that *High Times* recommended marijuana abstinence if a person developed CHS.

CHS was first reported in 2004 by Allen et al. The ten patients described there were all cyclical vomiters and chronic marijuana users. Nine of the ten also had the abnormal bathing behavior of multiple hot showers or baths. The symptoms of nausea, vomiting and abdominal pain would all settle within minutes of taking a hot bath or shower. Symptoms resolved with abstaining from marijuana use in seven of the ten patients. Three of the abstaining patients resumed marijuana use and relapsed within months.

CHS is a recurrent disorder, with symptom-free periods. There are three phases: pre-emetic, hyperemetic, and recovery. The pre-emetic phase can last for months or years. Patients have early morning nausea, a fear of vomiting and abdominal discomfort. They maintain normal eating patterns and may even increase their marijuana use because its reported relief of nausea.

The hyperemetic phase has spasms of intense and persistent nausea and vomiting, which has been described as "overwhelming and incapacitating." Patients vomit profusely, often without warning—up to five times per hour. There can be weight loss. Most patients have diffuse, but relatively mild abdominal pain. They are found to be dehydrated, but hemodynamically stable. The tests and work ups done at EDs are inconclusive in the majority of cases.

During this phase, patients take numerous hot showers throughout the day. As this seems to be the only measure that brings some symptom relief, it rapidly becomes a compulsive behavior. The precise mechanism for this relief is not known. It typically lasts for 24 to 48 hours, but the risk of relapse is high if the patient resumes cannabis use.

The recovery phase can last for days, weeks or months. It's associated with relative wellness and eating patterns. "Weight is regained and bathing returns to regular frequency."

Patients with CHS usually are misdiagnosed for a considerable length of time. One problem is that it is often confused with cyclic vomiting syndrome (CVS). "Confusion also exists in the medical literature secondary to a failure to recognize chronic marijuana use as a source of vomiting." Although there is a close similarity of conditions, there are also significant differences. You can read more about CHS at:

Allen et al. (2004) Cannabinoid hyperemesis: Cyclical hyperemesis in association with chronic cannabis abuse" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1774264/)

Galli et al. "Cannabinoid Hyperemesis Syndrome" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3576702/)

Kim et al. (2015) "Cyclic Vomiting Presentations Following Marijuana Liberalization in Colorado" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4469074/)

Abnormal Brain Structure, Poor Memory and Pot

A study published in the December 2013 issue of the journal *Schizophrenia Bulletin* found that two years after stopping marijuana use teens who were heavy marijuana smokers, smoking pot daily for about three years, had abnormal changes in their brain structures. This finding is suggestive of the potential long-term effects of chronic marijuana use. These marijuana-related brain abnormalities are correlated with "poor working memory performance and look similar to schizophrenia-related brain abnormalities."

Working memory is the brain's ability to process information in the moment and then transfer it to long-term memory—if we need to remember it. Poor working memory is predictive of poor academic performance and everyday functioning. One of the study's co-senior authors said: "This study very nicely extends the set of regions of concern [in addiction research] to include those involved with working memory and higher level cognitive functions necessary for how well you organize your life and can work in society." It sounds like the "stoner" caricature has been scientifically validated.

The younger the person was when they started daily marijuana use, the more abnormally their brain regions were shaped. This suggests that if the abuse starts at an early age, the effects of the drug on the brain areas related to memory may be worse. The subjects in the study who used marijuana did not abuse any other drugs.

Previous research has shown that marijuana abuse can be linked to schizophrenia (see the studies discussed below). Of the fifteen study participants with schizophrenia, thirteen started heavy marijuana use before they developed the mental disorder. While chronic marijuana smokers and chronic marijuana smokers with schizophrenia both had brain abnormalities related to the drug, those with schizophrenia had greater deterioration in the thalamus. The thalamus functions as the communication center of the brain and is also critical for learning, memory and communication between regions of the brain. One of the study's co-senior authors said: "This paper is among the first to reveal that the use of marijuana may contributes to the changes in brain structure that have been associated with having schizophrenia."

It is possible that the abnormal brain structures indicate a pre-existing vulnerability to marijuana abuse. So a longitudinal study is needed to definitively show if marijuana is responsible for the brain changes and memory impairment. "But evidence that the younger a subject started using the drug the greater his brain abnormality indicates marijuana may be the cause."

To read the original article, go to: "Heavy Marijuana Users Have Abnormal Brain Structure, Poor Memory." (https://www.sciencedaily.com/releases/2013/12/131216080454.htm)

In April 2014 another study published in *The Journal of Neuroscience* demonstrated that even casual users, smoking marijuana one to five times per week, can lead to changes in the size, shape and density of areas of the brain known as the nucleus accumbens and amygdala. These are two of the regions of the brain responsible for processing emotions, making decisions and motivation. The findings then support the well-known theory that marijuana use leads to amotivation (becoming less oriented towards goals and purposes in life; less focused). Although the study did not examine cognitive symptoms, the researchers believe the brain abnormalities in their study could lead to substantial effects on brain development and behavior, particularly among younger marijuana users. Further study is needed to confirm the findings, including: 1) longitudinal studies that follow people over time; 2) whether abstaining from marijuana use leads to these abnormalities going away; and whether smoking marijuana at different stages of life (like during the teen years) effects brain development. Given the social movement toward the legalization of marijuana, Dr. Hans Breiter, one of the study's authors, this research needs to occur quickly. "This study is just a beginning pilot study, but at the same time, the results that came out are the same as a canary in a coal mine. . . . The interaction of marijuana with brain development could be a significant problem."

The abstract for the journal article is available online here: (http://www.jneurosci.org/content/34/16/5529.abstract); as are two news articles discussing the study's results on LiveScience, "Even Casual Pot Use Changes the Brain and Fox News, "Casual marijuana use linked with brain abnormalities."

Brain Scans and Pot

A 2012 study by British researchers suggests that marijuana can mean different things to different people. Some people mellow out, while others become paranoid and anxious. A unique brain scan study suggests that two ingredients of marijuana tetrahydrocannabinol (THC) and cannabidiol (CBD) may work independently to achieve these effects.

The new study used functional MRI (fMRI) scans, which track brain activity in real time. It found that ingesting THC prompted a significant increase in paranoid and delusional thinking by boosting the brain's responses to otherwise insignificant stimuli, while reducing response to what would typically be seen as significant. The more that "normal" brain responses were set off-kilter, the more severe the paranoid or even psychotic the reaction.

The effect of CBD was nearly opposite. Ingesting CBD appeared to prompt brain activity linked to appropriate responses to significant stimuli in the environment. According to these findings, Dr. Sagnik Bhattacharyya suggested that marijuana played both a good and a bad role in the context of psychosis. CBD may have potential use for the treatment of psychosis, while THC raises the risk for developing psychotic complications.

Dr. Joseph Coyle, a professor of psychiatry and neuroscience at Harvard Medical School, said the current study helps to "connect the dots" in understanding the effects of marijuana.

> What we're talking about here is the kind of perception, in this case prompted by marijuana, that leads a person to think that other people who are just talking in the subway are all actually talking about him," he noted. "Or people who are just tipping their hat for no reason are actually doing so specifically about him. And so this paper strikes me as important, because it actually looks at this kind of increased anxiety and increased hyper-alertness which are major factors in psychosis -- and then finds out what's going on in the brain among people who experience them.

To read the original article this was taken from on Philly.com go to: "Paranoid or placid? Brain Scans show pot's effect on mind." To read the original research study, try: Bhattacharyya, S. (2012). "Induction of Psychosis by 9-Tetrahydrocannabinol Reflects Modulation of Prefrontal and Striatal Function During Attentional Salience Processing." *Archives of General Psychiatry,* vol. 69 (1): 27-36.

Marijuana and Brain Shrinkage

Australian researchers reported in the June 2008 edition of *the Archives of General Psychiatry* that long-term use of marijuana may cause two areas of the brain, the hippocampus and amygdala, to shrink in size. Brain scans of 15 men (an average age of 39.8 years) who had smoked at least five joints of marijuana daily for over 10 years (an average duration of 19.7 years) showed that their hippocampus was 12 percent smaller in volume, while their amygdala was 7 percent smaller, when compared to 16 men who were not marijuana users. The study also found the heavy cannabis users earned lower scores than the nonusers in a verbal learning task; when trying to recall a list of 15 words.

The hippocampus regulates memory and emotion, while the amygdala plays a critical role in fear responses (such as immobilization, rapid heart beat or increased respiration). It also modulates emotional arousal surrounding a memory, and therefore our recollection of the original event.

The marijuana users were more likely than nonusers to exhibit mild signs of psychotic disorders, but not enough to be formally diagnosed with any such disorder, the researchers said. Additionally, about half of the marijuana users reported experiencing some form of paranoia and social withdrawal, while only one of the nonusers reported such symptoms. The heavy marijuana users reported that they had used other illicit drugs less than 10 times, according to the researchers.

Murat Yucel of ORYGEN Research Centre and the University of Melbourne, who led the study, said that: "These findings challenge the widespread perception of cannabis as having limited or no harmful effects on (the) brain and behavior." He added that everyone is vulnerable to the potential problems, namely memory problems and psychiatric symptoms "if they use heavily enough and for long enough."

Bruce Mirken, a spokesman for Marijuana Policy Project (a group supporting legal sales and regulation of marijuana) challenged the study's findings, particularly because they

were based on men who were such heavy, long-term users. “This study says nothing about moderate or occasional users, who are the vast majority -- and the (study) even acknowledges this.”

For the original article: Yucel, M. et al. (2008). “Regional Brain Abnormalities Associated With Long-term Heavy Cannabis Use.” Archives of General Psychiatry, vol. 65 (6): 694-701. The above summary was also based upon a June 2nd 2008 report from Reuters by Will Dunham: “Heavy Marijuana Use Shrinks Brain Parts.”

Marijuana and Brain Function

A 2016 study by Columbia researchers found evidence of a compromised dopamine system in heavy marijuana users. Dopamine levels were lower in the striatum, an area in the brain involved in working memory, impulsive behavior and attention. Prior studies have found addiction to other drugs of abuse, such as cocaine and heroin, have similar effects on dopamine release. This was the first such evidence for marijuana:

http://www.science20.com/news_articles/heavy_cannabis_use_associated_with_reduced_dopamine_release_in_brain-170570

A press release by the Columbia University Medical Center, “Heavy Cannabis Users Have Lower Dopamine Release in the Brain,” quoted the lead author as stating that in light of the increasing use and acceptance of marijuana, especially by young people, it is important to look more closely at the potentially addictive effects of cannabis on key regions of the brain. The study was small, with 11 adults who were severely dependent upon marijuana and 12 matched healthy controls. The average age of onset among the marijuana users was 16, with dependence occurring by 20. In the month before the study, all users in the study had smoked daily.

“Compared with controls, the cannabis users had significantly lower dopamine release in the striatum, including subregions involved in associative and sensorimotor learning.” The investigators also explored the relationship between dopamine release in the striatum and cognitive performance on learning and working memory tasks. The bottom line was that long-term, heavy marijuana use could impair the dopaminergic system, which in turn could have a series of negative effects on learning and behavior.

Brain Research by MIND and Staci Gruber

There has been a series of articles documenting the findings from the research of Staci Gruber and the MIND project at McLean Hospital in Boston. MIND stands for: Marijuana Investigations for Neuroscientific Discovery. Currently MIND is conducting a longitudinal study of MMJ. The first phase of the MIND project assesses subjects at baseline, before beginning their MMJ treatment. They then track their use of marijuana (MJ) and are in touch with researchers biweekly. Follow up visits occur every three months for two years in order to assess the potential impact of MMJ on cognitive function and related brain and quality of life measures.

The second phase is an FDA-approved clinical trial of high-CBD sublingual tincture for treating anxiety. A third and final phase will examine the clinical state and cognition in veterans who are using cannabinoids to treat various conditions, including PTSD, insomnia and pain. The MIND website noted how policy has gone too far ahead of science, so there is little data available on the impact of MMJ on cognitive functioning.

> Given the considerable difficulty with cognitive function and disrupted mood experienced by patients with severe medical disorders, the addition of MJ, which has shown promise in alleviating a range of symptoms, could potentially improve cognitive performance. Equally critical, data showing a loss or impairment of cognitive function following the use of MMJ could inform alternative courses of treatment, staggered dosing, and ultimately prevent unjustified exposure to harm. As the number of states who have passed MMJ laws continues to grow, the 'need to know' has never been more important, relevant or timely, and has significant implications for public health policy.

Dr. Gruber has been doing research into the effects of MJ since the early 1990s and has documented some interesting neurological effects from MJ. She led a 2013 study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659424/) that found there were differences in the brain's white matter and impulsivity between teenagers and young adults smoked an average of 25.5 joints of MJ per week and a control group who did not smoke MJ. Their research suggested that in some individuals who begin smoking MJ at an early age, differences in brain function and structure emerge during development. The study sample was small and it was not clear if the brain changes resulted from MJ use or predated MJ use. The changes could have occurred as the result of either chronic MJ use or reflect a delay in brain development in MJ smokers.

> These data represent the first report of significant alterations in frontal white matter fiber tract integrity that are associated with self-report measures of impulsivity in chronic, heavy MJ smokers, and appear to be related to age of onset of MJ use. . . . Future investigations should include additional measures of behavioral impulsivity and their relationship to age of onset of MJ use to more fully explore the potential neurodevelopmental aspects of white matter changes in MJ smokers. Findings from this study suggest that changes in white matter microstructure may be predictive or associated with increased impulsivity, and may ultimately contribute to the initiation of MJ use or the inability to discontinue use.

A follow up study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3967072/) done by Gruber and others was published that same year, 2013. The study confirmed that heavy MJ smokers had lower levels of white matter in the corpus callosum region of the brain; and that earlier age of MJ use was associated with these lower levels of white matter. MJ smokers also had higher levels of impulsivity.

> Taken together, these findings reinforce the idea that early onset of MJ use negatively impacts white matter development and is associated with behavioral impulsivity, a combination that may have enduring negative

> effects, particularly on the developing brain. Data from this study highlight the importance of early identification of MJ use among emerging adults and the need for efforts aimed at delaying or preventing the onset of MJ use.

Then a third study (https://www.ncbi.nlm.nih.gov/pubmed/26997188) by Gruber and her research team at MIND published in the March 2016 issue of the *Journal of Studies on Alcohol and Drugs* found that MJ smokers had poorer executive brain function than the control group. The difference seemed to be primarily the result of early onset of MJ use, before the age of 16. The differences remained even after the frequency and amounts of MJ used were controlled. Additionally, the early MJ use and the greater amounts of MJ used predicted poorer performance and errors on the Wisconsin Card Sorting Test (WCST), which is used to assess abstract thinking. "The WCST is also considered a measure of executive function because of its reported sensitivity to frontal lobe dysfunction."

> These findings underscore the impact of early onset of marijuana use on executive function impairment independent of increased frequency and magnitude of use. In addition, poorer performance on the WCST may serve as a neuropsychological marker for heavy marijuana users. These results highlight the need for additional research to identify predictors associated with early marijuana use, as exposure to marijuana during a period of developmental vulnerability may result in negative cognitive consequences.

In 2018, Staci Gruber and Kelly Sagar published a review of the impact of marijuana on cognition, brain structure and function ("Marijuana Matters" in the journal *International Review of Psychiatry*: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6455965/). They noted how numerous studies have documented the effects of marijuana on a wide range of cognitive domains, including (but not limited to): various aspects of memory, executive function/working memory, processing speed, and overall intelligence. "There is general consensus that MJ particularly impacts memory and executive function adversely, and some evidence also suggests decrements in processing speed."

They reported that regular marijuana users often exhibit reductions in grey matter volume, in several brain regions, especially the hippocampus. Studies have found that structural alterations in a number of brain regions appear to be related to increased executive dysfunction. "Grey matter consists of neuronal cell bodies and is responsible for information processing and decision making."

Reduced white matter fiber tract integrity has been observed in several prefrontal, limbic, parietal and cerebellar tracts in adolescent and emerging adult marijuana users. White matter controls the signals that neurons share and is critical for coordinating efficient communication between brain regions. A relationship between earlier age of onset of marijuana use and lower white matter integrity has been reported. These alterations have also been correlated with impulsivity and appear to be a risk factor for poorer executive function.

A number of studies have reported that decrements observed in adults tended to be more significant or persist for longer periods of time in those who began using marijuana during adolescence. Some investigations have indicated that earlier age of marijuana onset appeared to be linked to higher frequency and amount of marijuana use, "suggesting that

increased marijuana use may be a trait characteristic specific to early onset users." So individuals with earlier marijuana onset may have an additive vulnerability, "marked by a brain that is susceptible to the impact of marijuana coupled with an increased likelihood to engage in higher levels of marijuana use, relative to those with later marijuana onset."

> Age of MJ onset is therefore an important variable to include in research investigations as individuals who begin using MJ during adolescence are characterized by relatively "immature" brains and a tendency to use MJ more regularly, potentially posing a greater risk for cognitive decrements.

Sagar and Gruber concluded:

> Decades of research have focused on the impact of recreational MJ use, documenting decrements across various cognitive domains (e.g., memory, executive function, and likely processing speed) as well as structural and functional brain alterations which often underlie poorer cognitive performance or suggest inefficient processing in chronic, heavy users. These changes are most evident among adolescent users or those with early onset of MJ use, as adolescence represents a critical period of neurodevelopment, making youth more vulnerable to exogenous influences, including MJ. Accordingly, frequency and magnitude of use, product choice/potency, mode of use, and age of the consumer are all likely to influence the effects of MJ on the brain. It is important, however, to recognize that cannabis is a diverse and complex plant comprised of numerous constituents, which exhibit unique effects when studied alone as well as in the presence of other cannabinoids. Despite the range of effects conferred by individual constituents, many of which are non-intoxicating and have no diversion potential, cannabis is currently treated as a single entity and classified as a Schedule I substance, the most restrictive drug class, significantly hindering research efforts. While recreational use among adolescents and early onset users is relatively well studied, a number of areas remain understudied. For example, future investigations are needed to clarify the impact of MMJ on the brain, short- and long-term consequences of high potency products and novel modes of use, effects of MJ use in older adults, and the efficacy and safety of existing products as well as those in development, ideally using clinical trial models. As the nation has warmed toward the idea of MJ for both medical and adult recreational use, the need for empirically sound data is critical to help patients and consumers make informed decisions about their use.

Marijuana and Psychosis

A July 2007 article published in the British medical journal *Lancet* indicated a relationship between marijuana use and psychosis. The authors reported that their analysis showed the risk of psychosis increased by 40% in people who have used marijuana even one time. An even greater risk was evident with the most frequent users, where the risk of psychosis was 50 to 200% greater than normal.

Theresa Moore and six other researchers completed what was called "the most comprehensive meta-analysis to date of a possible causal relation between cannabis use and psychotic and affective illness." Moore et al said: "We believe that there is now enough

evidence to inform people that using cannabis could increase their risk of developing a psychotic illness later in life." They also noted some evidence for an association between affective disorders (i.e., depression and anxiety) and marijuana use. "The evidence that cannabis use leads to affective outcomes is less strong than for psychosis but is still of concern."

The research evidence falls short of concluding a direct causal link between smoking marijuana and psychosis. But Moore states the relationship is strong enough to justify public policy changes, such as educational campaigns to alert people to the possible risks associated with cannabis. "The question of whether cannabis causes psychotic or affective disorders is perhaps the wrong one to be asking, because it will be difficult to answer with any degree of certainty." The ultimate proof of a causal relationship would require a large-scale placebo-controlled randomized trial of cannabis exposure in healthy young people, with long term follow up. Such a trial cannot be done because of the practical and ethical reasons involved. But there is some evidence in short term studies that cannabis is responsible temporarily for more severe psychotic symptoms, which is suggestive of a longer term causal effect of marijuana use on psychosis.

The evidence is strong enough that the editorial staff of *Lance*t acknowledged how in a 1995 editorial, they said, "The smoking of cannabis, even long term, is not harmful to health." However, research published sine 1995, including Moore's study, "leads us now to conclude that cannabis use could increase the risk of psychotic illness." For the original article: "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review," by Theresa H M Moore et al. *Lancet,* 2007, vol. 370, 319-28.

The results of a 10-year follow up study of 229 individuals diagnosed with schizophrenia demonstrated that cannabis use after the onset of schizophrenia was associated with more severe psychotic symptoms over the 10-year follow-up time. Exposure to cannabis before the initial psychotic episode predicted an earlier age for the first episode; and that the psychotic symptoms experienced at the time of the initial episode would be more severe. The link between cannabis use and psychotic symptoms was evident even after the researchers controlled for variables such as: depressive symptoms, other drug use, and demographic variables. The relationship with psychotic symptoms was also bidirectional: "cannabis exposure predicted severity of psychosis, and individuals with more severe psychotic symptoms were more likely to use cannabis in the future."

For the original article: "Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization," by Daniel J. Foti et al. *The American Journal of Psychiatry,* 2010, vol. 167, 987-993.

Another study in the *International Journal of Pharmacology,* "Cannabis Use and Mental Health: A Review of Recent Epidemiological Research," by T.H. Richardson concluded that there was evidence to suggest that cannabis could induce or exacerbate a number of mental health problems. Cannabis may be used to cope with the symptoms of depression. Yet it could increase the risk of later depression. Cannabis use for self medication of anxiety was said to be common. "The strongest evidence for a causal role of cannabis in anxiety is that it may induce panic attacks." Cannabis has been frequently used by individuals with bipolar

disorder and has been shown "to predict manic and hypomanic symptoms in the general population."

But the largest body of literature concerns the relationship between cannabis and psychosis. "Cannabis use considerably increases the risk of psychotic symptoms and diagnoses such as schizophrenia. There is little evidence that self medication accounts for this relationship. . . . More frequent use entails an elevated risk and early use increases the likelihood of psychosis and an earlier onset of psychotic symptoms."

The June 2014 issue of *Molecular Psychiatry* published an article entitled: "Genetic Predisposition to Schizophrenia Associated with Increased Use of Cannabis." The researchers found a significant correlation between cannabis use and schizophrenic risk alleles. While not conclusive proof, the findings are suggestive that the genes that increase the risk of psychosis increase the risk of cannabis use. "Although directly predicting only a small amount of the variance in cannabis use, these findings suggest that part of the association between schizophrenia and cannabis is due to a shared genetic aetiology."

Biological evidence supports a causal link between marijuana and psychosis. Additionally, this seems to be dose-dependent—with higher potency marijuana, there is an increased likelihood of a psychotic disorder. What is not clear, however, is whether at a population level patterns of cannabis use influence the levels of psychotic disorder. A new study published in *The Lancet Psychiatry* reported there is a strong link between high-potency marijuana and psychosis. "The odds of psychotic disorder among daily cannabis users were 3·2 times higher than for never users, whereas the odds among users of high potency cannabis were 1·6 times higher than for never users."

If an individual began using marijuana before the age of fifteen, the odds were slightly increased, but not independent of the frequency of use or the potency of cannabis used. Compared with individuals who never used marijuana, those who used high-potency marijuana daily had four-times higher odds of psychosis. People who were using high-potency marijuana doubled their risk of psychotic disorder. "Our results show that in areas where daily use and use of high potency cannabis are more prevalent in the general population, there is an excess of cases of psychotic disorder." The researchers estimated that 20% of the new cases of psychotic disorder could have been prevented if the daily use of cannabis had been arrested.

The study drew its data on first-episode psychosis cases from 17 areas in England, France, the Netherlands, Italy, Spain and Brazil. The novelty of this study was its multicenter structure and the availability of incidence rates for all the sites. The use of high-potency cannabis was a strong predictor of psychotic disorder in Amsterdam, London, and Paris where it was widely available. In the Netherlands the THC content can reach as high as 67%. See the chart below.

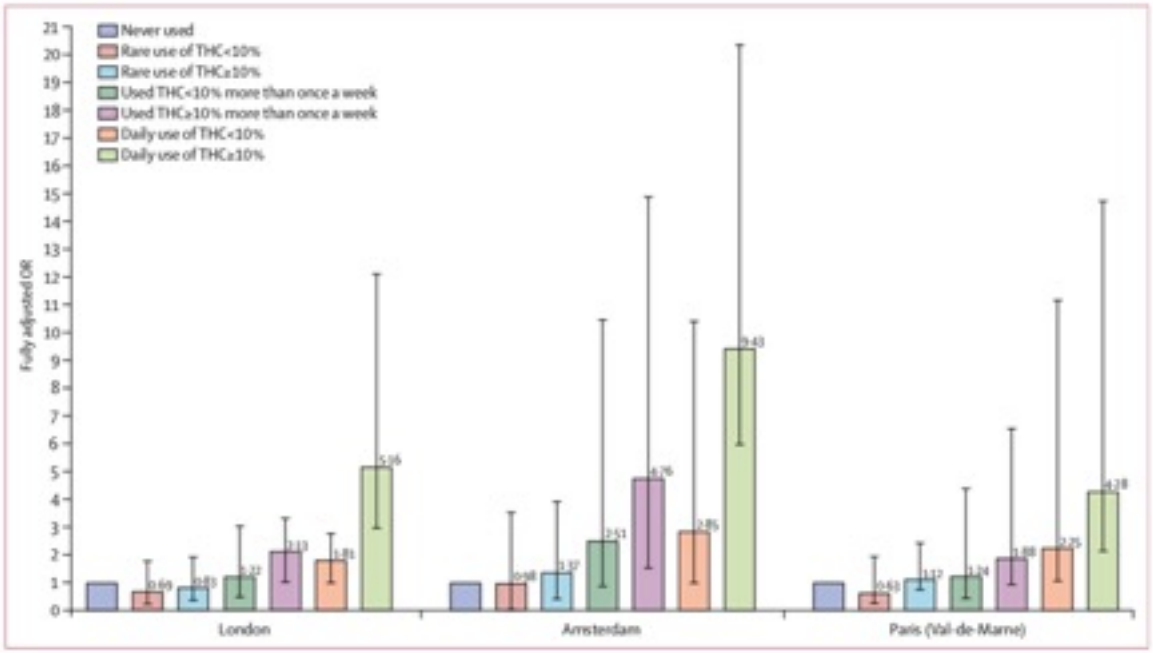

Figure 2: Fully adjusted ORs of psychotic disorders for the combined measure of frequency plus type of cannabis use in three sites
Data are shown for the three sites with the greatest consumption of cannabis: London (201 cases, 230 controls), Amsterdam (96 cases, 101 controls), and Paris (54 cases, 100 controls). Error bars represent 95% CIs. OR=odds ratio.

In conclusion, our findings confirm previous evidence of the harmful effect on mental health of daily use of cannabis, especially of highpotency types. Importantly, they indicate for the first time how cannabis use affects the incidence of psychotic disorder. Therefore, it is of public health importance to acknowledge alongside the potential medicinal properties of some cannabis constituents the potential adverse effects that are associated with daily cannabis use, especially of highpotency varieties.

Cannabis Use and Earlier Onset of Psychosis

A 2001 meta-analysis study reported in the *Archives of General Psychiatry,* "Cannabis Use and Earlier Onset of Psychosis," said there was little doubt of an association between substance use and psychotic illness. The authors noted that national mental health surveys have found an association between cannabis use and individuals diagnosed with a psychotic disorder. Some studies have even suggested that cannabis use is associated with an earlier onset age with psychotic disorders. Their own meta-analysis suggested there was a strong scientific evidence for an association between substance sue, particularly marijuana, and an earlier age at onset of psychotic illness. "The association between the extent of cannabis use in the substance-using group and the effect size as well as the weaker association between earlier age at onset and alcohol use support the hypothesis that cannabis use is a causal factor in psychotic disorders." The authors said that reducing cannabis use could delay and even prevent some cases of psychosis. "This finding is an important breakthrough in our understanding of the relationship between cannabis use

and psychosis. It raises the question of whether those substance users would still have gone on to develop psychosis a few years later."

Daily use, especially of high-potency cannabis is related to the earlier onset of psychosis in cannabis users. A 2013 study in the journal *Schizophrenia Bulletin,* "Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users," found that cannabis was associated with an earlier age of onset of psychosis. Individuals with a history of cannabis use had their first episode of psychosis at a younger age than those who had never used cannabis. Those individuals who had started using cannabis at age 15 or younger had an earlier onset of psychosis than those who had started cannabis after 15. Subjects who had been using a high-potency cannabis daily had the earliest onset of psychosis; an average of 6 years earlier than non-cannabis users.

Also look for: "Shatter and Psychosis" on this website.

Marijuana and Mental Health

In July of 2007, the Office of National Drug Control Policy released a survey of recent research into the association between marijuana and mental illness. "The Link Between Marijuana & Mental Illness: A Survey of Recent Research" in no longer available online, but is cited in several other sources. It contained brief summaries of research studies noting evidence for an association between marijuana use and depression as well as schizophrenia.

With regards to depression and suicide, a 16-year study published in 2001 showed that individuals who initially were not depressed and then smoked marijuana after the study began, were four times more likely to be depressed at the time of the follow up assessment. Two separate studies published in 2002 showed evidence of an association between marijuana and depression. One study looked at changes over a 14-year period of time and found that marijuana use was a predictor of individuals developing a major depressive disorder later on in life. Another longitudinal study over 21 years found that marijuana use was associated with depression, suicidal thoughts and suicide attempts. In 2007, an Australian study of young adults under the age of 21 found a relationship between early initiation and frequency of marijuana use and the symptoms of anxiety or depression. This was regardless of whether there was a personal or family history of mental illness.

Previously I noted the findings of Theresa H. M. Moore et al. in a Lancet 2007 article that concluded there was enough evidence "to warn young people that using marijuana could increase their risk of developing a psychotic illness later in life." Several studies in addition to Moore's were reviewed in the Office of National Drug Control Policy survey. A 2007 study that compared the brain scans of heavy or long term marijuana users and those of schizophrenics found similarities in the areas of the brain that show cognitive dysfunction, problems with thinking and reasoning. Another brain-scanning study found similar abnormalities in the brains of frequent adolescent marijuana users and adolescents with schizophrenia. These defects were in areas of the brain that continued to develop during

adolescence; parts of the brain associated with emotion and higher cognitive functioning such as language, perception, creativity, and problem-solving.

There is also some evidence for genetic predisposition or vulnerability to the effects of marijuana on mental health. "A study published in Biological Psychiatry found that as many as one in four people may have a genetic profile that makes marijuana five times more likely to trigger psychotic disorders." . . . "A 2006 review of six longitudinal studies in five countries found that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia."

College Students with Psychiatric Problems and Cannabis Use Disorder

At the 2014 annual meeting of the American Psychiatric Association, Meesha Ahuja of Brown University reported on research that showed college students with psychiatric problems and a cannabis use disorder had greater functional impairment than students with mental health issues without substance use problems. "Nearly half of the students with both cannabis use disorder and at least one other psychiatric diagnosis were on medical leave (46%), compared with 13% of those with a psychiatric illness but no substance use disorder." Bipolar disorder was the most frequent co-occurring diagnosis with cannabis use disorder. Forty-seven percent of students with bipolar disorder also had a cannabis use problem. Alcohol use disorder was also associated with increased impairment among the college students diagnosed with psychiatric disorders, but not as seriously as with cannabis use. Jeffrey Borenstein, MD, a psychiatrist from Columbia University said: "My concern with the movement to legalize marijuana is that it may encourage more people to experiment with marijuana and that may be dangerous for them." See the MedPage Today article, "Pot Overuse Plus Psych Issues May Signal Trouble."

Unexplained Death and Marijuana

A study by German researchers in *Forensic Science International*, "Sudden Unexpected Death Under Acute Influence of Cannabis," (http://www.medicinalgenomics.com/wp-content/uploads/2011/12/Sudden-unexpected-death-under-acute-influence-of-cannabis.pdf) has stirred up a firestorm of controversy as a result of their conclusion that two unexplained deaths were the result of acute cannabis influence. The case report described the cases of two young, healthy men who died unexpectedly under the acute influence of cannabinoids (THC). "To our knowledge, these are the first cases of suspected fatal cannabis intoxication where full postmortem investigations, including autopsy, toxicological, histological, immunohistochemical, and genetical examinations, were carried out." After excluding other possible causes of death, they assumed the man died from "arrthythimas evoked by smoking cannabis." HOWEVER, "this assumption does not rule out the presence of predisposing cardiovascular factors."

They noted the absolute risk of cannabis-related cardiovascular effects were low and that the cannabis-induced changes were transient. Yet they cited two studies indicating that the risk of myocardial infarction was elevated almost 5 times in the first hour after

smoking marijuana; and it declined rapidly afterwards. “Consequently, the relative risk of cardiovascular effects is most probably increased within this period.”

There was another alleged case of unexplained death from THC (http://www.huffingtonpost.com/2014/02/06/gemma-moss-marijuana-death_n_4738167.html), a young woman named Gemma Moss. A Colorado doctor who works with medical marijuana patients in that state said: “There’s no history of any reports of a death from cannabis ever.” He admitted that it could cause an increased heart rate, so there was a potential problem with someone with a pre-existing heart disease. “But there’s no known dose of cannabis that could kill a human.”

Well, there does seem to be a known dose of THC that would kill a human. The above noted report cited a 2009 study in *American Scientist,* The Toxicity of Recreational Drugs, suggested that using more than 1,000 times the effective dose of THC in marijuana would have to occur for possible fatalities. The fact that typical doses of THC were well below the supposed lethal dose was also noted by the German researchers.

“Nevertheless, it is impossible to predict how certain individuals respond to cannabis smoke, as underlying illnesses and complicating factors may be unknown. The presented case highlights the potentially hazardous cardiovascular effects of cannabis in putative healthy young persons.”

Marijuana and Sleep Problems

In June of 2014 a study done at the University of Pennsylvania suggested that marijuana use could be related to sleep problems, especially with people who have been using marijuana since their teens. “The most surprising finding was that there was a strong relationship with age of first use, no matter how often people were currently using marijuana.” People who started using before the age of fifteen were about twice as likely to have severe problems falling asleep, feeling overly sleepy during the day, or have non-restorative (light, restless, poor quality) sleep. The study was not designed to investigate causality, so the results are only suggestive of a relationship. However, the results have a clear importance for further research since marijuana is the most commonly use illicit drug in the U.S.; it has a high prevalence of use among teenagers; and marijuana is becoming legal in some states. According to Michael Grandner, PhD, “As more people have access, it will be important to understand the implications of marijuana use on public health, as its impact on sleep in the ‘real world’ is not well known.” See a news release about the study from Penn Medicine, “Penn Medicine Study Finds Marijuana Use May Impair Sleep Quality;” and one from the American Academy of Sleep Medicine, Marijuana Use is Associated with Impaired Sleep Quality.”

Marijuana Addiction and Withdrawal

Cannabis (marijuana) is the most widely used illicit drug in the U.S. and world. Since the early 1990s, drug and alcohol treatment admissions for marijuana have increased to the point that they are now comparable to admissions for cocaine or heroin. Although there is

clear evidence of a cannabis withdrawal syndrome, its diagnosis is excluded from the DSM IV reportedly because its "clinical significance is uncertain."

A number of findings have challenged that assessment. A majority adults and adolescents seeking outpatient treatment for cannabis dependence have difficulty achieving initial abstinence. Many of them complain that withdrawal contributes to their problems quitting; and they report using marijuana and other substances to alleviate the withdrawal symptoms. These withdrawal symptoms are observable by others, and comments by these observers suggest that the symptoms can be disruptive of daily living.

Most symptoms of marijuana withdrawal begin within the first 24 hours of cessation, peak within the first week and last between one and two weeks. The symptoms generally include: increased anger and aggression, anxiety, depressed mood, irritability, restlessness, sleep difficulty and strange dreams, decreased appetite, and weight. Headaches, physical tension, sweating, stomach pain, and general physical discomfort have also been reported, but are less common.

A research study by Vandrey et al. (2008), "A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances", investigated the withdrawal syndrome of individuals who were simultaneously smokers of tobacco and marijuana. Participants had to have a pattern of regular, heavy marijuana use (at least 25 days per month); smoke at least 10 cigarettes daily; and report maintaining this usage pattern for at least six months prior to the study.

The study compared the abstinence effects associated with cessation from cannabis only, tobacco only, and both cannabis and tobacco combined over a 5–day period of abstinence. Participants attended 30-minute sessions each weekday to obtain self–reported affective and behavioral measures, physiological measures, and staff–observed urine and breathe samples.

Results found that the following items from a Withdrawal Symptom Checklist were rated significantly higher by all the study's participants during the abstinence period: anxiety/nervousness, decreased appetite, depressed mood, difficulty concentrating, feverish, increased anger, irritability, physical discomfort, restlessness, shakiness, sleep difficulty, stomach pain, strange dreams, sweating, and tension. Significant withdrawal effects were observed for each of these symptoms except decreased appetite in the dual abstinence condition. However, clear differences in withdrawal symptoms were evident between the cannabis only and tobacco only groups.

Withdrawal symptoms reported by the cannabis abstinence group, but not the tobacco abstinence group included: decreased appetite, difficulty concentrating and strange dreams. Withdrawal symptoms reported by the tobacco abstinence group, but not the cannabis abstinence group included: increased anger, physical discomfort, restlessness, shakiness and tension. Withdrawal symptoms common to both groups were: anxiety/nervousness, irritability and sleep difficulty.

Significant conditions by day interactions were observed for ratings of difficulty concentrating, increased aggression, increased anger, irritability and sleep difficulty. Post hoc analyses indicated that ratings of difficulty concentrating were greater on days 4 and 5 in the tobacco and dual abstinence conditions compared with the cannabis abstinence

condition. Increased aggression, increased anger, and irritability were greater in the dual abstinence condition compared with the cannabis and tobacco abstinence conditions on day 2. Increased aggression was also greater in the dual abstinence condition compared with the cannabis abstinence condition on day 4. Sleep difficulty was greater in the dual abstinence condition compared with the tobacco abstinence condition on days 2 and 4.

Overall withdrawal discomfort and individual symptom severity during cannabis abstinence was similar to that observed during tobacco abstinence in the present study. The differences observed between the cannabis and tobacco abstinence conditions were mostly for symptoms expected to differ based on previous studies. Exceptions to this were that ratings of anger and craving appeared to be higher during tobacco abstinence compared with cannabis abstinence.

The authors concluded that the cannabis and tobacco withdrawal syndromes are of comparable severity. Their results were similar in magnitude to that observed in prior studies using similar measures; and consistent with their previously reported research in 2005, "A cross–study comparison of cannabis and tobacco withdrawal," published in The American Journal on Addictions.

At the 2008 annual meeting of the American Psychiatric Association, National Institute on Drug Abuse (NIDA) researcher David Gorelick reported that in a study of nearly 500 marijuana smokers, a total of 42.4 percent of the study's participants experienced a lifetime withdrawal syndrome. 95.5% of all subjects reported experiencing at least one of the 40 individual symptoms. 91.3% reported at least two; 85.1% at least three; 79.1% at least four; 73,6% at least five; and 43.1% ten or more. The commonest withdrawal symptoms were psychological: cannabis craving (75.7%), mood changes (33.7%-50.1%), sleep disturbances (21.8%-46.9%), and decreased appetite (38.8%). The duration of withdrawal symptoms was highly variable, ranging from 1.5 weeks to more than one year. 70.4 percent of those who reported withdrawal symptoms said they started smoking marijuana again to reduce them.

The study involved 469 marijuana smokers, ages 18 to 64, none of whom suffered from recognized psychiatric disorders. About one in four reported smoking marijuana more than 10,000 times; approximating 27 years of daily use. More than half included in the study smoked more then 2,000 times. "These were heavy users," Gorelick says. He added that heavy marijuana users should be prepared to experience an uncomfortable withdrawal syndrome when they try to quit. Gorelick predicted that cannabis withdrawal syndrome will be recognized as a psychiatric disorder in the next edition of the Diagnostic and Statistical Manual of Mntal Disorders (DSM), which is due out in 2012.

Levin, K., et al. "Cannabis Withdrawal Symptoms in Non-Treatment-Seeking Adult Cannabis Smokers, " *Drug and Alcohol Dependence*, 2010. The full text of the article is available online.

An identical report, Withdrawal Symptoms From Smoking Pot?, on the above study can be found at CBS News and Web MD.

Vandrey, R. G. et al. (2008)). "A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances." *Drug and Alcohol Dependence,* vol. 92, issues 1-3, January, pages 48-54.

"Prevalence and Correlates of DSM-5 Cannabis Use Disorder, 2012-2013: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions–III," an epidemiological study by Hasin et al., published in the *American Journal of Psychiatry*, concluded that cannabis use disorder was prevalent within the U.S. population. The study estimated that 2.5% of the U.S adult population— approximately 8 million people according to 2016 census estimates—met the criteria for cannabis use disorder in the 12 months prior to the survey. Over six percent (20.3 million) meet the criteria for a lifetime diagnosis of cannabis use disorder. The mean days of use per year were 225.3 and 274.2 respectively. Individuals with a cannabis use disorder were also likely to meet the criteria for an additional diagnosis, such as: other substance use disorders, affective disorders, anxiety disorders and personality disorders. "Only 13.2% with lifetime cannabis use disorder participated in 12-step programs or professional counseling."

Marijuana and the Heart

The April 2014 issue of the *Journal of the American Heart Association* published an editorial on recreational marijuana use: "Recreational Marijuana Use: Is It Safe for Your Patient?" The authors noted evidence for the association between marijuana use and several adverse cardiovascular effects, including angina, myocardial infarction, cardiac arrhythmias, and coronary no-flow. "In cases where marijuana use was linked to myocardial infarction, patients tended to be younger and have no other risk factors for infarction." Another cited study reported a significant 4.8-fold increase in the incidence of myocardial infarction in the first hour after marijuana use. Similarly, there was a 4.2-fold increase in the mortality rate observed in marijuana users compared with nonusers following myocardial infarction. Although there is evidence to suggest the therapeutic benefit of marijuana for a number of chronic, debilitating conditions, "clinical evidence also suggests the potential for serious cardiovascular risks associated with marijuana use." Read the editorial online.

Within the same April 2014 issue of the *Journal of the American Heart Association* was an article on a French study that suggested cannabis use may be a triggering factor for cardiovascular disease in young people, "Cannabis Use: Signal of increasing Risk of Serious Cardiovascular Disorders." The researchers looked at all the reported cases of cannabis-related events to the French Addictovigilance Network from 2006 to 2010 (1979). They intent was to describe all cases of cannabis-related cardiovascular complications and to assess whether there has been an increase in the risk of these events. Their data showed that during the 2006-2010 period that the proportion of cardiovascular complications rose from 1.1% to 3.6%. The complications were all serious, and included cardiac and extracardiac complications, mainly acute coronary syndromes and peripheral arteriopathies (the obstruction of large arteries *not* within the coronary, aortic arch vasculature or brain). They concluded that: "Cannabis may trigger cardiovascular complications and therefore should be regarded as so by health practitioners and by users, who often admit the danger of drugs like cocaine or amphetamines but minimize that of cannabis."

Thomas, Kloner and Rezkalla published an article in the January 2014 issue of *The American Journal of Cardiology* (http://www.ajconline.org/article/S0002-9149(13)01976-0/fulltext) describing a series of marijuana-related heart problems. These issues included: myocardial infarction, sudden cardiac death, cardiomyopathy, stroke, transient ischemic attack, and cannabis arteritis. The authors reviewed the cardiovascular and cerebrovascular effect of marijuana use. It also speculated on the underlying mechanisms to these adverse effects, while acknowledging that relatively little is known about the underlying mechanisms at this point in time. "In conclusion, the potential for increased use of marijuana in the changing legal landscape suggests the need for the community to intensify research regarding the safety of marijuana use and for cardiologists to maintain an awareness of the potential for adverse effects."

There was also a case report in the December 2001 issues of *Forensic Science International* by Bachs and Morland, "Acute cardiovascular fatalities following cannabis use," (http://www.fsijournal.org/article/S0379-0738(01)00609-0/abstract) of six possible cases of acute cardiovascular death in young adults, who had very recent cannabis use. This was confirmed by the presence of THC in post mortem blood samples; no other drugs were present.

In December of 2019, researchers published a study in the journal *JACC Cardiovascular Imaging* that found an association between regular current marijuana use and an enlarged left ventricle in the heart. The left ventricle is one of the hardest working and thickest sections of the heart. Changes to this section of the heart potentially can lead to heart problems and ultimately heart failure. They also found early signs of impaired heart function in current marijuana users, which they measured using the deformation of heart muscles during contraction. To the best of their knowledge, this was the first study to systematically report alterations in cardiac structure and function associated with recreational marijuana use, using cardiovascular magnetic resonance (CMR) parameters, the current gold standard for cardiac chamber assessment.

(https://www.sciencedirect.com/science/article/pii/S1936878X19310095?via%3Dihub)

Marijuana and Lung Cancer

An investigation done by Case Western Reserve University researchers into the association between marijuana smoking and lung cancer found that marijuana may cause precancerous changes in the lungs.

Various research studies since the 1960s have investigated whether smoking marijuana causes lung cancer, but the overall conclusion of these studies is unclear. Given that marijuana use is the most commonly used drug worldwide (according to the 2006 World Drug Report), and that over the last decade cannabis use is outpacing increases for opiates and cocaine, further efforts to investigate this potentially fatal association need to occur.

The Case Western researchers reviewed 19 previous studies from 1965 through October of 2005 that examined premalignant or cancerous changes in the lungs of persons who smoked marijuana. Within studies that examined these lung cancer risk factors, they found a link between marijuana use and certain changes in lung tissue that promote cancer.

These changes in lung tissue included oxidative stress, dysfunction of tumor-fighting cells, changes in tissue structure and DNA alterations. The changes among marijuana smokers were also greater than those among tobacco smoking or nonsmoking control subjects. However, after adjusting for concurrent tobacco use among the research participants of other observationally-based studies, the researchers failed to demonstrate a significant association between marijuana smokers and a diagnosis of lung cancer.

They noted several methodological problems with these observational studies that challenged the validity of generalizing their failure to show an association between marijuana smoking and lung cancer to others. One glaring error was the overall youth of the participants, which precluded sufficient lag time for lung cancer to have developed in the marijuana smoking participants. Additional concerns included a selection bias, small sample sizes, an inconsistent measurement of marijuana exposure, and the lack of a standardized method for diagnosing the presence of lung cancer among participants of the various studies. The researchers concluded:

> Although observational studies have not shown a substantive marijuana smoking–lung cancer association, these studies are fraught with serious methodologic limitations. Therefore, the combination of the widespread use of marijuana, potential marijuana-related health implications outlined in this review, and studies evaluating lung premalignant alterations supporting a biologically plausible association between marijuana smoking–lung cancer association. . . . Given the prevalence of marijuana smoking and studies predominantly supporting biological plausibility of an association of marijuana smoking with lung cancer on the basis of molecular, cellular, and histopathologic findings, physicians should advise patients regarding potential adverse health outcomes until further rigorous studies are performed that permit definitive conclusions.

A free pdf copy of this study, "The Association Between Marijuana Smoking and Lung Cancer," can be found in the July 10, 2006 issue of the *Archives of Internal Medicine* (vol. 166, no. 13).

Marijuana and Lung Damage

Researchers at the Medical Research Institute in New Zealand reported that smoking one joint caused lung damage equivalent to smoking 2.5 to five cigarettes in rapid succession.

The study originally sought to investigate whether smoking marijuana put smokers at a greater risk of developing emphysema. Participants were placed in one of four different groups: marijuana smokers, tobacco smokers, smokers of both marijuana and tobacco and nonsmokers. All volunteers were given tests and x-ray scans to assess the health status of their lungs and airways. All smokers in the study complained of coughs and wheezing, but only the tobacco smokers showed any signs of emphysema. Smoking marijuana was found to be associated with the impairment of large airways function leading to hyperinflation and airflow obstruction. The extent of lung damage found was directly related to the number of joints smoked; and the researchers calculated that "one joint of cannabis was

similar to 2.5 to five tobacco cigarettes in terms of causing airflow obstruction." They speculated the difference was due to how cannabis was smoked: usually without a filter and with its smoke at a higher temperature.

Further research at Medical Research Institute in New Zealand reported in January of 2008 that smoking one joint had the equivalent risk of smoking 20 cigarettes in terms of lung cancer risk. Cannabis smoke contains twice the level of carcinogens found in tobacco smoke. "Cannabis smokers end up with five times more carbon monoxide in their bloodstream (than tobacco smokers)," said Richard Beasley of the Medical Research Institute of New Zealand. Within a high–exposure group for lung cancer, individuals were interviewed in an attempt to find the primary risk factors for the disease. After adjusting for variables including cigarette smoking, the risk of lung cancer in this high–exposure group rose by 5.7 times for patients for patients who smoked more than a joint a day for 10 years, or two joints a day for 5 years. Beasley concluded that long–term cannabis smoking increases the risk of contracting lung cancer; and he predicted that in the near future we could see an "epidemic" of lung cancers in many countries associated with the carcinogens in marijuana because of the increasing use of marijuana among young adults worldwide.

See Aldington, S., et al. (2007) "The Effects of Cannabis on Pulmonary Structure, Function and Symptoms." *Thorax,* published online July 31, 2007; doi: 10.1136/thx.2006.077081.

For a summary of the study, also look at an article published online July 31, 2007 in *The Guardian*, "Cannabis joints damage lungs more than tobacco."

Marijuana smokers are also at greater risk of developing bullous lung disease, and exhibit symptoms at a younger age (approximately 20 years earlier) than tobacco smokers. Bullous lung disease is a rare type of respiratory distress usually found with advanced cases of emphysema. It functionally impairs typical pulmonary activity and leads to diminished exercise capacity and even acute respiratory distress. Most patients with bullae have a significant cigarette smoking history, although cocaine smoking, marijuana smoking and inhaled fiberglass exposure have been shown to be associated with emphysematous lung bullae.

See Hill, S, et al (2008) "Bullous Lung Disease Due to Marijuana," *Respirology*, vol. 13, issue 1, 122-127.

There have been some studies that demonstrate potential medicinal benefits of marijuana use. With the state-by-state movement to legalize medical, there is a need for quality scientific research into the claimed and potential medical benefits of marijuana. What follows are some articles that look at the medicinal benefits of marijuana. A few will also look at the concerns with marijuana as a medicine.

It has also become clear that the federal government needs to modify its resistance to reclassifying marijuana's Schedule I Controlled Substance status to allow more quality research into its use and to fund that research. Otherwise, the current circus of

inconsistent regulations from state to state, and unverified claims about the medicinal benefits of marijuana will have us back in the days of patent medicines, as far as marijuana is concerned.

Marijuana and Pain Relief

Marijuana used to treat pain can be traced back to ancient Chinese texts, dating to 2900 BC. By the end of the 19th century, over 100 publications on medicinal cannabis were published in Europe and the US. The medical indications were primarily for its hypnotic and analgesic effects. Several studies have suggested that marijuana can help decrease pain. Research also suggests that marijuana can enhance the effects of opiate pain medications, meaning that effective pain relief can be provided at lower opiate doses if the patient uses marijuana in conjunction with his pain medication.

A study reported in the November issue of the medical journal *Anesthesiology* investigated the pain relief potential of three dosage levels of THC (tetrahydrocannabinol), the psychoactive ingredient in marijuana. Fifteen healthy volunteers were given marijuana to smoke after they had capaicin (the chemical found in chili peppers) injected under the skin of their arms to induce pain. Some of the volunteers were given a placebo.

Five minutes after smoking the drug, none of the subjects reported any effect on their felt pain. However, 45 minutes later, those subjects who smoked the moderate dose of marijuana reported their pain was much better, while those who used the high dose said their pain was worse. But in partial consolation for their greater discomfort, they did feel "higher" than the moderately dosed volunteers. The low dose of marijuana had no delayed effects on pain relief.

The researchers cautioned that the results of their study should not be taken as supporting the analgesic efficacy of smoking marijuana. They had a small number of subjects, who were all healthy, and who were all experienced marijuana users able to tolerate the highest study dose of cannabis. "It is possible that clinically ill samples, especially cannabis-naive subjects, would have a different analgesic response and incidence of side effects when exposed to the effective dose found in this study."

For an html or pdf version of the article, go to: Wallace, M. Schulteis, G., and Atkinson, J. H. (2007). "Dose-dependent Effects of Smoked Cannabis on Capsaicin-induced Pain and Hyperalgesia in Healthy Volunteers." *Anesthesiology*, vol. 107 (5): 785-796.

In the *American Journal of Public Health*, Carr and Schatman wrote "Cannabis for Chronic Pain: Not ready for Prime Time." They said that objective data on the efficacy of cannabis for pain management are not very encouraging. While it can be helpful in relieving neuropathic pain, the magnitude of pain relief is typically contingent on the amount of THC. Higher-THC cannabis has its own issues, producing more cognitive side effects, "often rendering patients impaired at work and in activities of daily living." Evidence of efficacy for conditions other than neuropathic pain, such as: fibromyalgia, headaches and rheumatoid illnesses is less compelling.

Even cannabis's efficacy for cancer pain has been questioned, with a recent review noting that it may have potential use but that existing human studies are of poor

quality, limited size, and outdated. In defense of cannabis as an analgesic agent are studies suggesting that it may achieve synergistic analgesia when coadministered with opioids, and some investigations point toward an opioid-sparing effect.

See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6301389/

THC and Serotonin Levels

A study published in *The Journal of Neuroscience* found that a synthetic form of THC, the active ingredient in marijuana, was an effective antidepressant at low doses, but worsens symptoms at high doses. It has been known for many years that depletion of the neurotransmitter serotonin in the brain leads to depression, so SSRI antidepressants (Prozac, Celexa and others) work by increasing the levels of serotonin in the brain. This study offers the first evidence that THC, when given in lower doses, will increase serotonin.

The antidepressant and intoxicating effects of cannabis are due to its chemical similarity to natural substances in the brain known as "endo-cannabinoids," which are released under conditions of high stress or pain, explained Dr. Gabriella Gobbi, the lead researcher in the study. They interact with the brain through structures called cannabinoid CB1 receptors. This study demonstrates for the first time that these receptors have a direct effect on the cells producing serotonin.

Laboratory animals were injected with a synthetic cannabinoid and then given the Forced Swim Test—a test to measure "depression" in animals. The researchers observed that an antidepressant effect of cannabinoids was paralleled by an increased activity in the neurons that produce serotonin. However, increasing the cannabinoid dose beyond a certain point reversed the effects. "Low doses had a potent anti-depressant effect, but when we increased the dose, the serotonin in the rats' brains actually dropped below the level of those in the control group. So we actually demonstrated a double effect: At low doses it increases serotonin, but at higher doses the effect is devastating, completely reversed."

Dr. Gobbi was prompted to investigate the potential of marijuana as an antidepressant through anecdotal clinical evidence. She noticed that several of her patients suffering from depression used to smoke marijuana. Conversely, there was some evidence that people suffering with multiple sclerosis and AIDS showed an improvement in their mood disorder when they were treated with cannabis. "But there were no laboratory studies demonstrating the anti-depressant mechanism of action of cannabis."

The new study doesn't unequivocally show the antidepressant benefits of THC. Controlling the dosage of THC in natural cannabis, marijuana, is difficult. Other studies have shown the potential risk of developing psychosis from excessive use of marijuana (see the "Marijuana and Mental Health" section of this article). But it does suggest a new line of research into drugs that enhance the effects of the brain's natural endo-cannabinoids. "We know that it's entirely possible to produce drugs which will enhance endo-cannabinoids for the treatment of pain, depression and anxiety."

See the original article by: Bambico, F. R., et al. (2007). "Cannabinoids Elicit Antidepressant-Like Behavior and Activate Serotonergic Neurons through the Medial Prefrontal Cortex." *The Journal of Neuroscience,* 27 (43): 11700 – 11711.

Blurred Boundaries

Marijuana has been used as a folk medicine as far back in time as five thousand years ago. The first medical use likely occurred in Central Asia and spread from there to China and India. The Chinese emperor Shen-Nung is known to have prescribed it in 2800 BC. Between 2000 and 1400 BC it came to India, and from there to Egypt, Syria and Persia. The Greeks and Romans valued marijuana as hemp for ropes. Europeans ate its seeds and used its fibers to make paper. An urban legend falsely held that the U.S. Constitution, Declaration of Independence, and Bill of Rights were written on hemp paper. All three were actually written on parchment.

An Irish doctor, W. B. O'Shaughnessy, working in Calcutta in the 1830s, wrote a paper on the medical uses of cannabis, which were strikingly similar to those known today—vomiting, convulsions and spasticity. By 1854, the medical use of cannabis was listed in the US Dispensatory. Nineteenth-century physicians had cannabis tinctures and extracts for ailments from insomnia and headaches to anorexia and sexual dysfunction. "Cannabis-containing remedies were also used for pain, whooping cough, asthma, and insomnia and were compounded into extracts, tinctures, cigarettes, and plasters."

The above short history on the history of medical marijuana was taken from an article in Mayo Clinic Proceedings by J. Michael Bostwick, "Blurred Boundaries: The Therapeutics and Politics of Medical Marijuana." He noted how the term medical marijuana refers to botanical cannabis, which contains hundreds of compounds—including the two most often used medicinally, THC and cannabidiol. Synthetic cannabinoids are produced in a laboratory. Botanical cannabis attracts the notoriety and controversy—because it is the same substance used recreationally by "stoners" to get high.

Bostwick noted how the recreational and medical marijuana use of marijuana is not always distinct, which has medical implications for both seasoned and naïve users. For example, naïve users may decide to stop using medical marijuana because of the psychoactive effects of the THC. Although most users will experience a mild euphoria, a few experience dysphoria, anxiety and even paranoia.

> As cannabis strains are bred that amplify THC content and diminish counteracting cannabidiol, highs become more intense but so do degrees of anxiety that can rise to the level of panic and psychosis, particularly in naive users and unfamiliar stressful situations.

The Bostwick article reviewed the often-blurred relationship between medical and recreational users, noted a Canadian study that found medical cannabis use often followed recreational use; and that most medical users continued using marijuana recreationally. Another study of 4100 Californians found that medical users preferred inhaling their medication. Smoked cannabis has a more rapid response and is easier to titrate so that users get the analgesic effects without the higher levels favored by recreational users

seeking the high. Given some of the medical problems from smoking marijuana, using vaporizers or nasal sprays may be an effective alternative delivery system.

Clearing Away the Smoke

Grant et al. reviewed evidence on the medicinal usefulness of marijuana in "Medical Marijuana: Clearing Away the Smoke." They noted that most of the studies on the efficacy and safety of cannabinoids for pain and spasticity have occurred since the year 2000. A series of randomized studies at the University of California Center for Medicinal Cannabis Research (CMCR) found that cannabis significantly reduced pain intensity. A significantly greater proportion of individuals reported at least 30% reduction in pain on cannabis; the threshold of decreased pain intensity generally associated with improved quality of life. Medium doses of 3.5% THC cannabis cigarettes were as effective as higher dose (7% THC).

Oral preparations of synthetic THC (dronabinol, Marinol) and a synthetic THC analogue (nabilone, Cesamet) are legally available. Studies suggest that dronabinol significantly reduces pain. The effects on spasticity are mixed: "there may be no observable change in examiner-rated muscle tone, but patients report significant relief." There has been less research done with nabilone, but there have been reports of modest analgesia. Dronabinol and nabilone are FDA-approved for control of acute and delayed nausea and vomiting from cancer chemotherapy.

Alternative delivery systems for cannabis include vape-pens, sublingual devices, and others that use a metered spray device. The advantages to such systems seem to be the use of known cannabinoid concentrations, predetermined dosing portions, and time-out systems that may help prevent overuse.

There are side effects, which are dose-related in terms of severity. Grant et al. reported that they seem to decline over time and are of mild to moderate severity. "Reviews suggest the most frequent side effects are dizziness or lightheadedness (30%-60%), dry mouth (10%-25%), fatigue (5%-40%), muscle weakness (10%-25%), myalgia [muscle pain] (25%), and palpitations (20%)." There is little data on a timeline of adverse or therapeutic effects. There have been concerns that rapid tolerance to adverse effects may indicate a corresponding tolerance to beneficial effects. But studies of oral sprays in multiple sclerosis report that you can reduce the incidence and severity of adverse effects by downward self-titration without loss of analgesia.

There are additional adverse effects, including some psychiatric side effects, especially with cannabis having high concentration of THC. See the original article for more specifics. The longer-term health risks of medicinal cannabis are unclear; most of the current evidence is based upon non-medical use. Some medical professionals indicate that effective medicinal use of cannabis requires significantly less marijuana than is typically consumed by recreational users.

Current Status of Medical Marijuana in the U.S.

In "The Current Status of Medical Marijuana in the United States," Gerald McKenna noted how the majority of medical marijuana users in Hawaii claim they have chronic pain. He said a main problem in getting the medical profession to support the use of medical marijuana is that it is not widely used medicinally in a non-smoking form. "Authorizing use by inhalation of a drug with an unknown number of co-drugs contained in the same raw form is not supportable." He said that supporting the use of medical marijuana by inhalation because users prefer it is akin to supporting the inhalation of any other drug taken orally. His impression is that medical marijuana laws have been passed "to bypass the illegality of marijuana."

He did recommend removing marijuana from Schedule I controlled substance so research could be done more easily. "Until that research is done, stating that marijuana is useful for treating chronic pain, anxiety, post-traumatic stress disorder, depression, and other health conditions remains anecdotal and conjectural."

Labeling Issues with Edible Cannabis Products

Vandrey et al. in a *JAMA* research letter, "Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products," reported on edible cannabis products that they purchased from three randomly selected dispensaries in three cities: Los Angeles, San Francisco, and Seattle. Of the 75 different products purchased from 47 different brands, only 17% were accurately labeled with respect to their THC content. Twenty-three percent were underlabeled (contained more THC than claimed on the label); and 60% were overlabeled (contained less THC than claimed on the label). Some of the overlabled products contained negligible amounts of THC.

The non-THC content of tested products was generally low. Forty-four products (59%) contained detectable levels of CBD. But only 13 had their CBD content labeled. Four products were overlabeled and nine were underlabeled.

See: https://jamanetwork.com/journals/jama/fullarticle/2338239

Cannabinoids for Medical Use

In "Cannabinoids for Medical Use," Whiting et al. did a systematic review and meta-analysis of randomized clinical trials of cannabinoids for various conditions: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity from multiple sclerosis or paraplegia, depression anxiety disorder, sleep disorder, psychosis, glaucoma or Tourette syndrome. They concluded there was moderate-quality evidence for the use of cannabinoids to treat chronic pain and spasticity. There was low-quality evidence to support using cannabinoids for nausea and vomiting dur to chemotherapy, weight gain in HIV infection, sleep disorders and Tourette syndrome. Cannainoids were also found to be associated with increased risk of short-term adverse events such as: dizziness, dry mouth, nausea, fatigue, drowsiness, euphoria, vomiting, disorientation, confusion, loss of balance and hallucination.

Is the Cart Before the Horse?

Doctors D"Souza and Ranganathan wrote an editorial for the same issue of *JAMA*, "Medical Marijuana: Is the Cart Before the Horse?" They raised the concern Whitling et al. found that for most of the indications that qualify by state law for medical marijuana, the evidence supporting its use is of poor quality. "For most qualifying conditions, approval has relied on low-quality scientific evidence, anecdotal reports, individual testimonials, legislative initiatives, and public opinion." So state and federal governments should support and encourage research so that high quality research on medical marijuana can be done for the conditions for which the existing evidence is insufficient or of poor quality.

They also noted how there are inconsistencies from state to state in how conditions are qualified for medical marijuana use. One example noted was that posttraumatic stress disorder was approved as a qualifying condition in some, but not all states. Unlike most FDA-approved drugs, marijuana has over 400 compounds; and there isn't a uniform composition of the cannabis preparations. "Given the variable composition, patients will have to experiment with different strains and doses to achieve the desired effects," a process known as titrating. The patient is looking for the personal Goldilocks dose—not too high and not too low.

While the acute adverse effects are known, the effects of repeated exposure, as would occur with medical marijuana needs further study. The risk of addiction, and a smaller risk of psychotic disorder were discussed. The interaction of marijuana with other drugs concurrently prescribed needs further study. They suggested that medical marijuana be added to monitoring databases along with opioids and benzodiazepines, so doctors would have a more complete understanding of the medication profile of their patients.

The human endocannabinoid system is involved in a variety of physiological processes such as appetite, pain-sensation, mood and memory. And there are two known cannabinoid receptors, CB_1 and CB_2. THC is a direct "fit" with the CB_1 receptor, while another cannabinoid, cannabinol fits with CB_2. The receptors are predominantly found in the brain (CB_1) and the immune system (CB_2). Cannabidiol (CBD) does not directly fit with either receptor, but has powerful indirect effects that are still being studied. See this graphic representation of the human endocannabinoid system.

"Emerging evidence suggests that the endocannabinoid system is critical in brain development and maturation processes, especially during adolescence and early adulthood." This ongoing development of the system during adolescence then raises questions on what age exposure to medical marijuana is justifiable. Brain development continues until the age of 25. "Changes in the endocannabinoid system have been linked to affective, behavioral, cognitive and neurochemical consequences that last into adulthood."

> In conclusion, if the states' initiative to legalize medical marijuana is merely a veiled step toward allowing access to recreational marijuana, then the medical community should be left out of the process, and instead marijuana should be decriminalized. Conversely, if the goal is to make marijuana available for medical purposes, then it is unclear why the approval process should be different from that used for other medications. Evidence justifying

marijuana use for various medical conditions will require the conduct of adequately powered, doubleblind, randomized, placebo/active controlled clinical trials to test its short- and long-term efficacy and safety. The federal government and states should support medical marijuana research. Since medical marijuana is not a life-saving intervention, it may be prudent to wait before widely adopting its use until high-quality evidence is available to guide the development of a rational approval process. Perhaps it is time to place the horse back in front of the cart.