Medicinal Marijuana, Stress, Anxiety, and Depression: *Primum non nocere*

by Mark Gold, MD

Medications are viewed as dangerous until proven safe and effective by science and approved by the FDA. Drugs of abuse are taken for many other purposes but often considered safe until proven unsafe.

Higher levels of stress are associated with an increased risk of substance use disorders (SUDs) and other mental health conditions like depression. Stress may exacerbate underlying medical and psychiatric conditions and weaken individual response systems that process events and build resilience. Stress can also make licit and illicit substance use more appealing as a quick self-treatment for anxiety. Stress may also cause SUD slips and relapse in patients who are in treatment for opioid and other substance use disorders. Deaths of despair,[1] including overdoses, have increased during the pandemic.[2]

The use of cannabis, vaping, or other tetrahydrocannabinol (THC) products may carry unique risks for those "self-medicating" and make depression worse when used as an ersatz antidepressant.[3] So-called 'medical marijuana' shouldn't be so lightheartedly rendered or prescribed as a relaxation tool. Short and long term changes in mood, depression, and suicidality can begin during adolescence and exacerbate by teen marijuana use according to a recent study.[4] This longitudinal cohort study of over 30 years found that cannabis use during adolescence is not a medicine, but is associated with both depression and suicidality in adult life. Early use is the riskiest. The younger the user of regular cannabis, the higher the risk of depression in adulthood. Recent use of marijuana for pain has also had unintended consequences, not replacing opioids but adding cannabis and even *de novo* cannabis use disorders to opioid risks.

Adults and youth with pain have heard and read claims about cannabis smoking or THC vaping for non-opioid pain relief. However, they are vulnerable to adverse cannabis outcomes, including continued opioid use and the development of additional substance use disorders.[5] Public "medicinal" opinions on hydroxychloroquine and actual FDA- quality studies of safety and efficacy in SARS COVID 19[6] or voting marijuana a medicine is quite different than proving in a prospective, random assignment, placebo-controlled double-blind studies. FDA standards protect us from unsafe and ineffective drugs and require that studies are specific to a particular disease at a precise dose and by a particular route and also superior to existing FDA treatments for that disease. While hopes for cannabis-derived medicines are rational, medicinal claims are premature.[7]

While not approved by the FDA for pain relief, it might have seemed logical to think and hope that medicinal marijuana would reduce opioid use. On the contrary, when studied, medical marijuana users are significantly more, rather than less, likely to use and misuse prescription drugs.[8] Drugs of abuse are unique in that they stimulate their taking but also because they all cause euphoria, loss of self-control, and self-administration through virtually the same net effect on the brain's dopamine systems. So even drugs initially supported by evidence of effectiveness may later prove to be more harmful than beneficial. Recommending marijuana as if it was an FDA approved and tested medication is currently a topic of great concern, debate, and consternation. *Primum non-nocere*, i.e., first do no

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harm. Medications are viewed as dangerous until proven safe and effective by science and approved by the FDA. Drugs of abuse are taken for many other purposes but often considered safe until proven unsafe. The reversal in the burden of proof means that drugs of abuse are field-tested en masse and consequences discovered over time. Vaping is a recent disastrous example.

Smoking and Vaping Marijuana and THC

The University of Michigan's Monitoring the Future reported that in 2019 (www.monitoringthefuture.org), there was a significant increase in daily cannabis use in the younger grades. Medicinal re-branding of marijuana smoking has accelerated trends in teens' perceptions of the risks of marijuana use; teens' view of risks has steadily declined over the past decade. In 2019, 11.8% of 8th graders reported marijuana use in the past year, and 6.6% were considered current users. Among 10th graders, 28.8% had used marijuana in the past year, and 18.4% were current users. Marijuana use among 12th graders is surprising since 35.7% had used marijuana during the year before the survey, and 22.3% used in the past month. An especially alarming, 6.4% of current high school seniors use marijuana daily or near-daily. Marijuana use is now at a 35-year high for college students. Daily or near-daily use of marijuana was 5.8% in 2018 for college students. It has been between 4% and 6% in the past five years. Among same-age non-college youth, it was 11.1%, nearly double the level for college youth. NIDA's Director Volkow[9] has discussed these findings, concerns of cannabis use disorders, and likely health, memory, and performance problems caused by regular marijuana use. With the growing popularity[10] of vaping, teens have increased vaping THC, with nearly 4% of 12th graders saying they vape THC daily. The use of tobacco, nicotine, and THC products is widespread among teens. Marijuana use has many adverse consequences, especially for children and teens, whose use is considered dangerous.[11]

Rates of cannabis smoking and vaping are similar to those reported for cigarettes, and cigarette smoking is related to marijuana use. Cannabis and tobacco use and misuse frequently co-occur,[12] and in some cases, cannabis smoking precedes tobacco smoking, and in others, tobacco smoking precedes marijuana smoking. THC use is also rising in many states that have legalized the substance, and among the young, for whom the effects of THC are different and likely more dangerous than they are for older individuals. The NIH's 2019 Monitoring the Future survey also found a spike in rates of youth vaping marijuana, concerning because of the substance and the risky delivery route. Learning to inhale drug vapors may be the gateway event worth additional study.[13] Most of the public health attention has been focused on vaping THC and death or severe toxic effects on lung and pulmonary function. The field testing of THC vaping and e-cigarettes have led to the CDC recommending no use of all e-cigarette or vaping, THC, and nicotine products.[14] Many more current and potential consequences of cannabis smoking and vaping THC are coming to light. Marijuana use has increased in teens following the reduction in perceived danger, ballot initiatives, and largely unproven medical marijuana claims.[15]

Whether it's logical to use alcohol or THC products for stress relief, instead of exercising or meditating or taking a walk or doing yoga or talking to a friend or therapist, is a different question from why some individuals do it. People often report anxiety as a primary motivation for using THC

Adolescent cannabis exposure results in impaired cognition, sleep, and driving ability.

products, and it isn't hard to find someone who will swear by the substance as a tranquil godsend without which life would be far less exciting and considerably more fraught. Researchers have focused more recent cannabinoid stress and anxiety efforts on inhibition of monoacylglycerol lipase (MAGL) to enhance signaling of the most abundant and efficacious endocannabinoid ligand, 2-arachidonoylglycerol (2-AG). Preclinical evidence supports a role for this system in the regulation of anxiety-related outcomes and stress and anxiety in the brain (doi:10.1016/j.biopsych.2020.01.015). Many research groups are hopeful that this work will provide us with answers to the question of why some individuals turn to marijuana for acute stress relief only to find that their stress and anxiety may make smoking cannabis or vaping THC more reinforcing.

Marcus et al. found[16] that a molecule, called 2-AG, helps create and move stress-related chemicals in the brain. These chemicals move along a brain path that connects the amygdala, which handles emotion, to the prefrontal cortex, which helps us make decisions. When individuals experience more stress, this path between the amygdala and prefrontal cortex becomes more active. The molecule works to manage stress and anxiety by limiting the chemicals that pass through the connecting path. 2-AG is part of the brain's anxiety-managing endocannabinoid system, in which the effects of marijuana are also felt. The brain's anxiety-limiting molecule and marijuana operate through the same receptors. In this study, researchers made mice stressed through exposure to foot shocks and bad odors. Then they observed the mice's brains and behavior to measure the effects of 2-AG and the path connecting the amygdala and prefrontal cortex. They found that making the mice stressed inhibited the effects of the molecule's ability to limit anxiety and led to more activity in the connecting path as the mice behaved more anxiously. These new findings indicate that more substantial levels of stress interfere with 2-AG's effects on blocking anxiety, overwhelming the endocannabinoid system and allowing anxiety-related chemicals to speed through the brain.[17]

Why Is This New 2-AG Study So Important?

Cannabis use proponents claim it is a medicine and treatment for anxiety, stress, pain, and also the opioid crisis. It is easier to make claims of safety and efficacy than to prove them. A formal study may determine safety and effectiveness, but in the meantime, cannabis has many advocates who argue that it is as good as any medication or therapy for anxiety and stress. But, no one has provided the kind of evidence that would be presented to the FDA as part of a new drug application. These claims have not been studied in random assignment, double-blind or comparable efficacy scientific trials. In the interim, it is safer to conclude that this also is not true.

This new study[17] finds specific pathways in the brain that lead to anxiety—especially the impairment of 2-AG—and suggests that new medications could be designed to work on this system to be more effective anti-anxiety medication. The authors of this study hope to do more research on how the cannabinoid system becomes impaired after stress exposure, how it repairs its anxiety-limiting function after impairment, and which molecules are involved in these processes. Well-functioning cannabinoid systems have a critical role in stopping or limiting anxiety. Genes and specific efforts to support this system like exercise,[18] diet, meditation, may explain why some individuals exposed to extreme stress or trauma don't develop severe mental health conditions. This research refers to stressed-out mice, not humans. Again, only further study can prove any of this.

Risks and Concerns

Advancements in the understanding of the endogenous cannabinoid system, neuroscience, and pharmacology of cannabis have led to numerous proposed uses. Medical cannabis is now legal in a majority of states, and THC and cannabidiol (CBD), the prominent cannabinoids found in cannabis, have both been utilized in the development of FDA-approved drugs. Medicinal claims and cannabis legalization have been influential and related to the emergence, and frequency of cannabis use disorders.[19] Cannabinoid exposure in rat adolescence reprograms the initial behavioral, molecular, and epigenetic response to cocaine.[20] Smoking marijuana for problems with pain management may result in a new substance use disorder without any change in the underlying disease or relief. As cannabis marketing, legal status and clinical studies of cannabis-related 'medications' continue, physicians are often lost without FDA guidance and will need to balance the real potential of these compounds with their limitations and adverse effects.[21]

Early exposure to cannabinoids in adolescent rodents decreases the reactivity of brain dopamine reward centers later in adulthood. To the extent that

In a recent survey, marijuana use among 12th graders is disturbing and concerning: 35.7% had used marijuana during the year before the survey, and 22.3% used in the past month.

these findings generalize to humans, this could help explain the increased vulnerability for addiction to other substances of misuse later in life that most epidemiological studies have reported for people who begin marijuana use early in life. It is also consistent with animal experiments showing THC's ability to "prime" the brain for enhanced responses to other drugs. For example, rats previously administered THC show heightened behavioral response not only when further exposed to THC but also when exposed to other drugs such as morphine—a phenomenon called cross-sensitization. Adolescent cannabis exposure results in impaired cognition, sleep, and driving ability. Cannabis Use Disorders are increasing, especially in teens and young adults, as a result of escalating use and consequences. Supportive and traditional behavioral therapies are currently the mainstay of treating cannabis misuse, with no pharmacotherapies presently approved by the FDA for cannabis use disorder in youth.[22]

Medicinal Cannabis and CBDs

There are no FDA-approved cannabinoid medications approved for psychiatric disease or even for the treatment of psychiatric symptoms. But, we have learned a great deal and have more to learn about marijuana as a medicine and CBD. The FDA has recently approved Epidiolex or CBD oral solution for the treatment of seizures associated with tuberous sclerosis and previously approved for the treatment of seizures associated with two other rare and severe forms of epilepsy, Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS). Epidolex is the only FDA-approved drug that contains a purified drug substance derived from cannabis. That means the FDA has concluded that this particular drug product is safe and effective for its intended use. The FDA has also approved Marinol and Syndros, medications which include a synthetic delta-9-tetrahydrocannabinol (dronabinol, THC) for the treatment of anorexia associated with weight loss in AIDS patients. Some valid researchers are optimistic that pharmaceutical-grade cannabinoids may be found through additional controlled study to be a useful medication for other diseases. CBD has also been shown to have promise as a treatment for specific distressing symptoms, especially in patients with precipitated craving and anxiety.[23] This does not mean that it is safe and effective for stress management, anxiety, depression, and other problems that can and are safely treated by psychiatrists and other health providers with approved and well-studied evidence-based approaches. Developing better tools to manage stress and anxiety makes the most sense. Developing better coping mechanisms is likely to be especially beneficial for individuals using risky

substances. Research continues to suggest that smoked or vaped marijuana or THC is one of these hazardous substances. As Harvard's Kevin Hill, MD,[24] has said recently, "Medical cannabis may ultimately prove to be effective in treating many other medical conditions, including posttraumatic stress disorder and Tourette syndrome, but as yet, there is little evidence to show that this is the case."

The risks of marijuana smoking and THC vaping are mostly unknown, but no news is not necessarily good news. Many substances, like marijuana, without overdose death risks, are considered safe because we can not imagine all of the ways that they can be dangerous. Of course, edibles have gained in popularity because it is evident that smoking exposes everyone to second hand (SHS) and third-hand smoke risks. SHS or "second hand" designation a sanitized way to say exposure to carcinogen-polluted air or intoxication without permission (doi:10.1371/journal.pone.0153327) and second-hand tobacco smoke is a significant cause of death each year. Inhaling someone's smoke vapors is a major second-hand problem, but there are other concerns like impaired drugged driving. Traffic accidents are increasing in cities and states where cannabis is legal and widely used. A recent study found that individuals using cannabis are worse drivers.[25] Impaired driving ability in tested simulations included crossing the centerline, speeding, hitting pedestrians, and missing stop signs. Study participants who started using cannabis before the age of sixteen fared even worse.

Cannabis use is presented in the media as a stress-relieving substance, a mostly harmless escape from life's ups and downs. It's also portrayed as an option to alcohol for those seeking an alternative to relaxation, meditation, or exercise to unwind chemically. Scientists rarely evaluate these urban myths, and once one is evaluated, a new claim is made for a new problem of modern living in real-time. A person may initiate cannabis smoking or vaping THC, believing that they may be self-medicating stress and anxiety. But, not only has this not been proven to work, but, if anything, research suggests that it is not a treatment but a significant risk.

Many more cannabinoids are likely to be approved as medicines, but it is not clear at this time as to which cannabinoid, in what dose, by which route, and in what disease. The role of cannabis in medicine is expanding, often with claims preceding testing. Use is not without other risks. One risk identified in new studies that cannabis and several cannabinoid-based medications may make other drugs of abuse more reinforcing.[26] Marijuana use is also linked to other substance use disorders, including alcohol and nicotine addiction.[27] Many findings are consistent with the idea of marijuana as a "gateway drug." The majority of people who use marijuana do not go on to use other "harder" substances. It may be becoming clear that current marijuana use makes cocaine and other drug use more reinforcing. New studies have suggested that parental use may cause such sensitization in their children to opioids.[28] Cross-sensitization is not unique to marijuana. Alcohol and nicotine also prime the brain for a heightened response to other drugs and are, like marijuana, also typically used before a person progresses to other, more harmful substances.[29]

Conclusion

It may be useful to recall that alcohol and tobacco[30, 31, 32] are not medicines, but medicinal uses were proposed for them. The U.S. Treasury Department, during prohibition, authorized physicians to write prescriptions for medicinal alcohol for cancer, GI distress, and depression. Of course, alcohol is not a safe and effective medicine for these problems and may cause them. The same may be true for cannabis claims and effects. Medicinal applications that are advertised or made for cannabis typically would require a pharmaceutical company to prove the treatment works for a specific illness. Physicians might wonder or ask if alcohol, tobacco, or cannabis can ever be called medicines without FDA approval? This cannabis- as-medicine process and outcome have made it easier to argue with the FDA over the definition of a medicine. Should we decide if hydroxychloroquine or cannabis is a medicine for COVID-19 by utilizing the FDA or by asking elected officials? A prescription should be tested rigorously in dose-safety – efficacy studies, successfully navigate the entirety of the FDA's new drug approval process and utilize modern science to separate therapeutic molecules from the smoke. Sure we might think about eating or smoking foxglove but is quite toxic. Digoxin was isolated from the foxglove plant, and Digitalis has become a great addition to the treatment of heart diseases recognized by the World Health Organization on its shortlist of safe, effective, and "Essential Medicines." Decriminalizing or legalizing adult recreational cannabis, like Budweiser or alcohol,[33] is one thing, but physicians and the public in short-circuiting the FDA protections are another. Short-

circuiting science from the new medicine decision-making process is a slippery slope. The 18th Amendment or National Prohibition Act enforced the ban on alcohol with a few specified exceptions. It allowed physicians to prescribe alcohol for most any ailment, farmers to produce wine for their consumption, and Clergy to provide alcohol during ceremonies. In his book on alcohol prohibition,[34] the author writes: "Presumably, doctors were doing examinations and diagnoses, but it was mostly bogus." Much remains to be settled about the claims, safety, and efficacy of cannabis. The FDA has just approved CBD again, this time for the treatment of seizures associated with tuberous sclerosis. Many more clinical trials are in progress. It is logical to expect pharmaceutical companies to successfully translate cannabinoid science to make new treatments and classes of medicines. In the meantime, Physicians should insist on science and data first, FDA controlled studies, and "First do no harm."

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