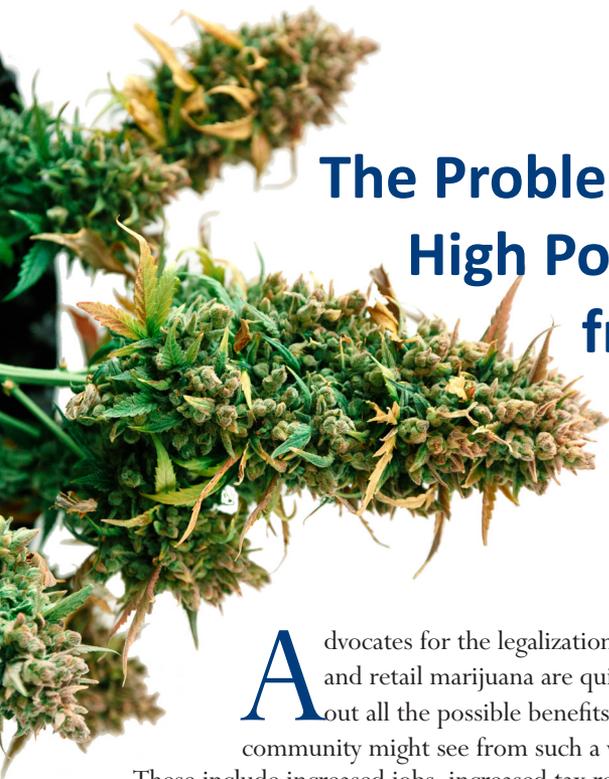


# The Problem with the Current High Potency THC Marijuana from the Perspective of an Addiction Psychiatrist

by Elizabeth Stuyt, MD



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

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



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

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

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

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

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

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

The reasons why adolescents are at such great risk for developing an addiction to drugs or alcohol is because this is a period with increased neurobiological based

tendencies for risk taking with decreased suppressive and regulatory control, and this is a period of decreased parental monitoring and increase in peer affiliations, a “perfect storm.”

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

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

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

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

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

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

A study in New Zealand with a 20-year follow-up showed an average loss of 8 IQ points with early persistent teen use of marijuana.<sup>19</sup> If you already have a high IQ, a drop in 8 points may mean the difference between making As and making Bs, however for the person with an average IQ of 100 (50<sup>th</sup> percentile), a loss of 8 points can put that person in the 29<sup>th</sup> percentile with significant difficulty in functioning. A study out of Yale University tracked 1,142 students who achieved similar SAT scores and were enrolled in college.<sup>20</sup> They found that those who used minimal alcohol or cannabis had an average GPA of 3.1 at the end

of the semester. Those who drank alcohol without using marijuana had an average GPA of 3.03 and those who used both alcohol and marijuana had an average GPA of 2.66.

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

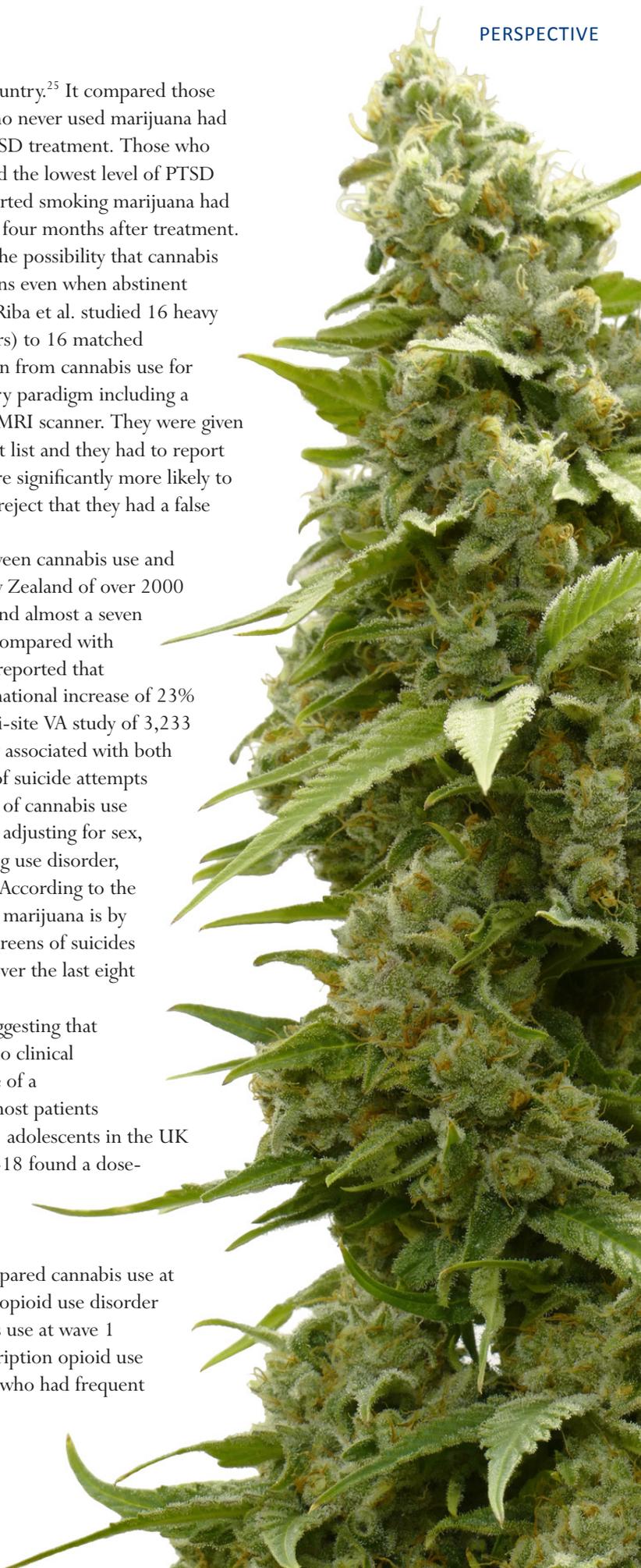
Numerous studies have demonstrated that using cannabis prior to the age of 15-18 significantly increases the risk of developing psychotic symptoms.<sup>23</sup> The risk is dose dependent and increases with greater frequency of use and with higher potency THC. A landmark study out of the UK analyzed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

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

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

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

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



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

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

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

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