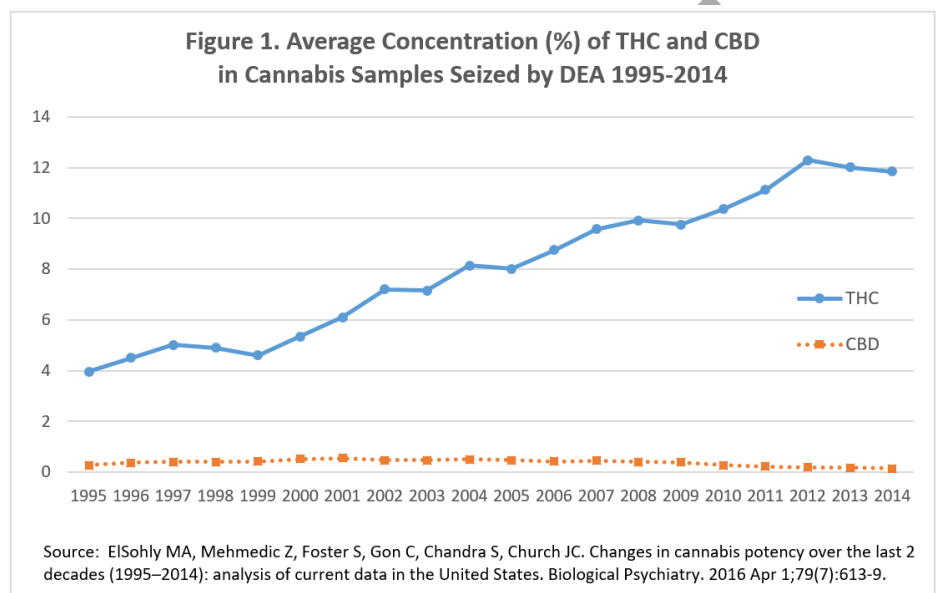




system (CNS) while CB2 expression is low in the CNS but high in peripheral immune cells and tissues.<sup>10</sup> Psychoactive effects of marijuana are attributed to CB1 receptors whereas CB2 receptors are non-psychoactive.<sup>9, 10</sup>

Aside from THC, the most studied phytocannabinoid is cannabidiol (CBD).<sup>11</sup> CBD has been described as nonpsychotropic due to the fact that it appears to be non-intoxicating and non-reinforcing, but it does appear to be psychotropic insofar as it appears to have pharmacological benefits with regard to anxiety, schizophrenia, addiction, and depression.<sup>12</sup> Table 1 summarizes the major CNS and cardiovascular effects of THC and CBD.<sup>11</sup> CBD has been demonstrated to attenuate certain effects of THC, including intoxication, sedation, and tachycardia.<sup>11</sup> In modern clinical trials, this has permitted the administration of higher doses of THC in an effort maximize therapeutic effects while minimizing side effects.<sup>11</sup> It is largely unknown how the interaction of THC and CBD plays out in practical use of marijuana by medicinal and recreational marijuana users.

Research on cannabis products seized by the US Drug Enforcement Agency (DEA) shows that the potency of marijuana in common use has increased dramatically in the last 2 decades, at least in terms of THC content.<sup>8</sup> As shown in Figure 1, from 1995 to 2014, the average THC content of seized cannabis products virtually tripled from approximately 4% to approximately 12%.<sup>8</sup> On the other hand, average CBD content fell from approximately 0.28% in 2001 to < 0.15% in 2014, resulting in a change in the THC:CBD ratio of 14:1 in 1995 to approximately 80:1 in 2014.<sup>8</sup> This means that, on average, the cannabis products seized in 2014 were presumably far more



intoxicating and than those seized in 1995 – and marijuana and cannabis products that are in common use may bear little resemblance to marijuana supplied by the federal government for marijuana research.<sup>13</sup> In terms of strength, the National Institute on Drug Abuse considers less than 1% to be low, 1-5% to be medium, 5-10% to be high, and over 10% to be very high.<sup>14</sup> An examination of the online menu of one of Seattle’s most popular recreational marijuana stores in June 2017 listed over 100 varieties of marijuana “flowers” that were labeled as 20% THC or higher, with THC content going as high as 30%. For many of these, CBD content was not listed. By comparison, there were only 20 varieties with listed THC content under 10%. Marijuana concentrates were labeled as having THC content as high as 97%. From a scientific standpoint, the effects of cannabis products with such levels of THC on mental health have largely not been studied.

Individual differences in objective and subjective effects of marijuana vary by individual, variety/strain, dosage, route of administration, personality, degree of tolerance, and other factors.<sup>9</sup> Many of the psychological effects of cannabis and THC are biphasic and bidirectional.<sup>9</sup> Acute marijuana intoxication is generally associated with euphoria, subjective quickening of associations, relaxation, decreased motor activity, a sense of calm, increased awareness of sensory experience and internal sensations of the body, transient sensory experiences, synesthesia, craving sweet and salty foods, enhanced perception of current activities, increased salience of stimuli, simultaneous focus on multiple things, impaired shifting of focus, fantasies of power, and belief of having arrived at a transcendent insight.<sup>15</sup> With regard to neurocognition, marijuana intoxication is associated with deficits in processing speed, attention, working memory, decision-making, motivation, time-perception, and reality testing.<sup>15</sup> Considering the broad range of effects, one can begin to imagine how marijuana could have beneficial or harmful effects with regard to mental health.

Tolerance to certain effects of marijuana develops with regular use, within several days in some cases,<sup>9</sup> as a function of CB1 receptor expression downregulation.<sup>10</sup> Research suggests that after tolerance develops it can take several weeks of THC-free recovery for CB1 receptor expression to return to baseline levels.<sup>10</sup> Because of tolerance, the

eventual downregulation of CB1 receptors with chronic use means that any benefit derived from THC with regard to mental health could result in symptom exacerbation when users are not under the influence of THC.<sup>10</sup>

## The Role of the Endocannabinoid System in Anxiety

The endocannabinoid system is expressed in all brain regions that are important for the processing of anxiety, fear, and stress and has been identified as playing an important role in these responses.<sup>16,17</sup> Recently, the molecular, cellular, and circuit mechanisms underlying the central role that cannabinoid signaling in the brain and body has in the control of stress, fear, and anxiety have begun to be elucidated.<sup>17</sup> Both for anxiety and fear memory processing, the endocannabinoid system is thought to ensure an appropriate reaction to stressful events and to serve as a regulatory buffer system for emotional responses.<sup>18</sup>

Endocannabinoids appear to modulate highly interactive stress and reward networks, consisting of the endocannabinoid system (ECS), dopamine system, and hypothalamo-pituitary-adrenocortical axis. These networks establish the balance between distress and well-being. Like social interaction and exercise, marijuana intoxication produces a sought-after state of calmness or contentedness, mediated by interactive anxiolytic effects of increased cannabinoid and oxytocin receptor activation and rewarding effects of elevated dopamine. Conversely, cannabis withdrawal is associated with lower ECS tone, partially mediated by release of stress hormones and reduced dopamine levels.<sup>10</sup>

## Marijuana Intoxication and Anxiety

Relaxation or tension reduction is commonly identified as a marijuana use motive<sup>19</sup> or effect expectancy.<sup>20</sup> On the other hand, anxiety and panic reactions are the most commonly noted negative acute effects of marijuana intoxication.<sup>21</sup> Crippa et al.<sup>21</sup> reviewed the literature on the relationship between marijuana intoxication and anxiety. They found the risk of anxiety being induced by marijuana intoxication was associated with the following factors: individual and genetic vulnerability, personality traits, female gender, infrequent use, high dose, high THC/low CBD varieties, history of previous anxiety reaction, presence of anxiety disorder/symptoms, basal anxiety state, abstinence states, and environment and context of use.

All other things being equal, THC appears to decrease anxiety at lower doses and increase anxiety at higher doses. Such an effect was observed in a recent study in which participants were exposed to a well-validated psychosocial stress task.<sup>22</sup> A low dose of THC (7.5 mg) reduced the duration of negative emotional responses to the task and post-task appraisals of how threatening and challenging the stressor was. In contrast, a higher dose of THC (12.5 mg) produced small but significant increases in anxiety, negative mood and subjective distress at baseline before and during the psychosocial stress task.<sup>22</sup>

CBD, on the other hand, appears to have robust anxiolytic effects without anxiogenic effects at higher doses. In fact, the anxiolytic effects of CBD in humans were first demonstrated in the context of reversing the anxiogenic effects of THC.<sup>23</sup> Human studies show that 300-600 mg of oral CBD reduces experimentally induced anxiety in individuals without anxiety disorders and reduces anxiety in patients with social anxiety disorder.<sup>23</sup> Notably, effects have only been demonstrated acutely; further studies are needed to establish the efficacy of CBD in reducing anxiety with chronic dosing.<sup>23</sup>

## Medicinal Use of Marijuana for Anxiety

As of June 2017, anxiety is not specifically listed as a qualifying condition for a medical marijuana card in any of the states that allow for medicinal use of marijuana.<sup>24</sup> In a study of a sample of 1,746 patients from a network of nine medical marijuana evaluation clinics in California, 37.8% of patients reported that they used marijuana to relieve anxiety, 16.9% to relieve panic attacks, and 55.1% to improve relaxation.<sup>6</sup> Anxiety/depression was identified by a physician as a reason for authorizing medicinal marijuana (MM) use on 13.0% of these patients' MM patient ID cards.<sup>6,25</sup> A recent study surveyed 1429 MM users recruited through social media and MM dispensaries from December 2013 to January 2016 in Washington State about the conditions they used MM to treat, use patterns, perceptions of

efficacy, and physical and mental health. More than half (58.1%) reported they used MM for anxiety. In general, participants indicated that they felt MM improved their symptoms of anxiety.<sup>26</sup>

In 2016, Walsh et al.<sup>7</sup> reviewed the literature on the use of MM for anxiety and concluded that evidence from cross-sectional studies generally supported the anxiolytic effects of MM. The researchers identified 8 cross-sectional studies that reported anxiety reduction as a primary or secondary benefit of MM. One of these studies noted that retrospective reports indicated that symptoms of anxiety returned upon cessation of MM use. When considering marijuana for the treatment of anxiety disorders, it should be remembered that regular marijuana use would result in tolerance to medicinal effects, thus increasing the risk of rebound anxiety upon cessation and fostering cannabis dependence.<sup>10</sup> To date, there have been no reported randomized controlled trials to show sustained benefits of cannabis in the treatment of anxiety disorders.<sup>10</sup>

## Relationship between Marijuana and Anxiety Disorders

A 2016 investigation of using the US National Epidemiologic Survey on Alcohol and Related Conditions with over 34,000 respondents examined prospective associations between marijuana use and risk of anxiety disorders, mood disorders, and substance use disorders in the general adult population.<sup>27</sup> In unadjusted analyses, in which covariates were not taken into account, cannabis use at Wave 1 was associated with increased prevalence and incidence of a broad range of anxiety and mood disorders at Wave 2, including all of the anxiety disorders (panic disorder, social anxiety disorder, specific phobia, and generalized anxiety disorder). However, after adjusting for several covariates (family history of substance use disorder, disturbed family environment, childhood parental loss, low self-esteem, early onset anxiety, social deviance, education years, trauma past year, Axis I comorbidity, Axis II comorbidity, ever divorced, history of alcohol use disorder, history of other drug use disorder, history of nicotine dependence, age, gender, non-White), cannabis use was associated only with increased prevalence and incidence of alcohol and drug use disorders, not any of the anxiety disorders.

A 2014 meta-analysis of 31 studies investigated the association between anxiety and cannabis use and use disorders in the general population.<sup>28</sup> Using data from approximately 112,000 individuals from 10 countries, results indicated small positive associations between anxiety and cannabis use and cannabis use disorders, even after controlling for demographics, other substance use, and other psychiatric comorbidity.<sup>28</sup> A subsequent meta-analysis had similar findings.<sup>29</sup> Any causal direction for the relationship between marijuana use and use disorders on the one hand and anxiety and anxiety disorders on the other hand is difficult to establish, and the evidence on the direction of causality is equivocal. Some longitudinal studies have shown frequent marijuana use precedes the development of anxiety disorders, others indicate that diagnoses of anxiety disorders precede marijuana use or use disorders, and others show no association.<sup>7</sup>

Among the anxiety disorders, social anxiety disorder (SAD) the one most associated with problematic marijuana use; SAD is correlated with marijuana dependence at rates more than twice that of other anxiety disorders, including generalized anxiety disorder, agoraphobia, and panic disorder.<sup>30</sup> Buckner et al.<sup>31</sup> examined the temporal relationship between SAD and cannabis use disorder (CUD) controlling for baseline CUD and other relevant variables including other anxiety disorders. Results indicated SAD may serve as a risk factor for subsequent cannabis dependence. The investigators suggested that their findings may indicate that individuals with SAD may be more likely to use marijuana to self-medicate anxiety reactions compared to individuals with other anxiety disorders. They point out that, for example, individuals with panic disorder have been found to avoid cannabis out of concern that use of cannabis bring about a panic attack. A recent study indicated that psychiatric outpatients with comorbid SAD and CUD reported better physical health, fewer limitations due to physical health, and a trend toward better adolescent and current psychosocial functioning than did those with SAD alone.<sup>32</sup> The researchers suggest that marijuana use may alleviate some SAD-related impairments in the short-term but also present increased risk of harm in the long term, especially in terms of likelihood of alcohol and other substance use disorders.

## Conclusions

In summary, effects of marijuana on anxiety disorders are complex. The endocannabinoid system appears to play an important role in responses to stress and anxiety. The two primary active ingredients of marijuana, THC and CBD, appear to have differing effects with regard to anxiety. Pure THC appears to decrease anxiety at lower doses and

increase anxiety at higher doses. On the other hand, pure CBD appears to decrease anxiety at all doses that have been tested. There appears to be tolerance to these effects over a short period of time with regular use. There are individual differences in responses to marijuana that are affected by a variety of factors. Many people report using marijuana to cope with anxiety, and this may be particularly common among those with social anxiety disorder. Those who are concerned about marijuana increasing anxiety are unlikely to use it whereas those who use it and find it to be beneficial presumably continue to use marijuana. Doing so may offer some benefit in the short term, at least in terms of anxiety, but well-controlled studies indicate that use of marijuana is associated with increased likelihood of substance use disorders in the future.

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