What are the effects of increasing cannabis potency on adolescent health?

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Summary

Cannabis is the most prevalent illicit drug amongst adolescents worldwide. Over the past 40 years, changes in cannabis potency (rising concentrations of delta-9-tetrahydrocannabiol, 'THC' and/or decreases in cannabidiol, 'CBD') have occurred. Epidemiological and experimental evidence demonstrates that cannabis with high THC and little if any CBD is associated with an increased risk of psychotic outcomes, an impact on spatial working memory and prose recall, and increased reports of severity of cannabis dependence. However, many studies have failed to address adolescence, the peak age at which individuals typically try cannabis - and may be the most vulnerable age to experience cannabis harms. In this review, we highlight the importance of changing cannabis products on adolescent health, and the implications for policy and prevention as legal cannabis markets continue to emerge worldwide.

Introduction

Cannabis is the most widely used illicit drug worldwide, with approximately 183·3 million users, making up nearly 4% of the global population[1]. Despite a decline in prevalence of use, cannabis is being used with greater frequency, for instance, in the United States, one in seventeen 12th graders (17-18 years) reported daily cannabis use, a rate that has increased since 2007[2]. It is estimated that 13 million people worldwide meet clinical criteria for a Cannabis Use Disorder - a problematic pattern of persistent use causing clinically significant impairment or distress - accounting for a global burden of disease of two million disability adjusted life years[3]. This burden peaks in late adolescence (age 20-24) and is highest in the United States, Canada, Australia, New Zealand and Western European countries such as the United Kingdom[3]. In Europe, the number of first-time clients entering specialist drug treatment for cannabis increased from 43,000 in 2005 to 76,000 in 2015[4] with rising trends in 16 of the 22 European countries providing eligible data[5]. While the explanation for this is unclear, it may be due to factors such as greater detection rates, improved pathways for referral, and changes in stigma towards mental health and treatment. An alternative explanation, however, suggests that this may be a result of an increase in cannabis potency (rising delta-9-tetrahydrocannabinol; 'THC' and/or decreasing cannabidiol; 'CBD')[6]. In light of widespread policy change in parts of the USA and Canada, resulting in the legalisation of medicinal and recreational cannabis (potentially changing the availability of cannabis products to millions of young people) and marked increases in the potency of cannabis products[7,8], understanding the effects of variation in cannabis potency on adolescent mental health, cognition, and development is of paramount importance. This will not only inform etiologic models of cannabis use and psychiatric comorbidity but will also allow for the design of evidence-based prevention programs targeting adolescent cannabis use. The World Health Organization (WHO) defines adolescence

as ranging between 10-19 years and young people as ranging between 10-24 years. This review includes research referring to both adolescents and young people recognizing the significance of shifting social determinants on later adolescent development[9].

Firstly this review will focus on the role of cannabis on the endocannabinoid system, commonly discussed cannabis constituents, and global trends in cannabis potency. Secondly, we will examine whether adolescents appear to be more susceptible to rising levels of THC (and/or lower levels of CBD) in cannabis. Thirdly, we will review evidence concerning the possible impact of increasing cannabis potency on adolescent neurocognition and mental health. Lastly, the review aims to highlight the importance of cannabis potency within clinical and educational policy and practice as well as making recommendations for future research.

Global changes in cannabis potency and cannabis markets

The effects of cannabis and its exogenous cannabinoids (including THC and CBD) occur primarily through interaction with the endocannabinoid system[10]. The endocannabinoid system includes cannabinoid receptors (CB1R and CB2R), their endogenous ligands including anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and enzymes such as Fatty Acid Amide Hydrolase, which breaks down AEA and 2-AG. The endocannabinoid system regulates numerous biological processes involved in development and neuroplasticity early in life, as well as playing a critical role in regulating synaptic plasticity[10]. CB1Rs are densely located in key brain regions involved in cognition, reward, and adolescent neurodevelopment such as the hippocampus, basolateral amygdala, nucleus accumbens, and the prefrontal cortex (PFC)[11]. With it occupying a broad spatial area of the developing brain, the endocannabinoid system plays a key role in age-related changes in the brain throughout the lifespan[10]. During the im-

portant time of neuromaturation, the brain may be more vulnerable to disturbances from exogenous cannabinoids, which may have a supraphysiological effect on endocannabinoid receptors, and thus alter normal brain functioning[12].

While cannabis contains a wide range of cannabinoids, the most commonly discussed are THC and CBD. THC acts as a partial agonist at CB1 receptors, while cannabidiol (CBD) has low affinity for CB1R, but can attenuate CB1R agonist effects and inhibit the reuptake and hydrolysis of endocannabinoids[11]. THC is the main psychoactive component responsible for the 'high' users seek, and has been found to have dose-dependent effects on memory, attention, and verbal fluency, as well as contributing to transient paranoid-like symptoms in laboratory studies[13]. By contrast, CBD is non-intoxicating and has been found to offset the harmful effects on verbal memory impairment and psychotic symptoms[14,15]. Concentrations of THC and CBD are known to vary across cannabis plants due to variation in genetics, growing conditions, preparation and extraction[16,17]. For instance, unfertilized female plants yield a more potent product, as the plant converts its energy to cannabinoid synthesis rather than seed production[18]. Referred to as sinsemilla (Spanish for "without seeds") (see Fig. 1), and commonly called 'skunk' in the UK or 'nederwiet' in the Netherlands, this highly potent type of cannabis has been found to contain THC ranging from 1·9% to 22·5% (Mean 14%), with minimal CBD[19]. A less potent type, seeded herbal cannabis, can range between 1·8% and 5·7% THC (Median 3.5%), whereas resin, compressed preparations of plant matter, can vary greatly in THC content (0% - 29·3% Mean 6.3%). An emerging cannabis product that is less common, but often extremely potent, is cannabis concentrates (see Fig. 1). Concentrates are produced via a range of extraction techniques (including butane, super-critical carbon dioxide, and combined heat and pressure), and as a result, differ in texture and appearance. They have also been found to vary greatly in THC and CBD, according to the extraction technique.

One particular study[20] in the US assessed the CBD and THC content of 57 concentrate samples at a medical cannabis market. It was found that they contained between 23·7% and 75·9% THC (Mean 63.4%), with all but five samples having low levels (<5%) of CBD[20].

In addition to recent advances in cannabis production and extraction techniques, New Psychoactive Substances (NPS) have also entered the drug market[21]. Synthetic cannabinoids elicit cannabimimetic effects similar to natural cannabis. However, while THC acts as a partial agonist, synthetic cannabinoids typically act as full agonists at cannabinoid receptors[22]. As a result, synthetic cannabinoids produce physiological (e.g. nausea) and psychiatric (e.g. anxiety, psychosis) effects that are considerably more intense than cannabis[22], and can result in more serious adverse events such as seizures and even death[23]. A thorough discussion of synthetic cannabinoids is beyond the scope of this review, which focuses on cannabis and its constituent cannabinoids.

The cannabis market in the US, Australia, and parts of Europe have shown to be dominated by high potency cannabis with high levels of THC and little if any CBD[8,17,19,24]. Over the past 40 years, THC levels in cannabis have steadily increased worldwide, with average THC in 2009 being over nine times greater than in 1970[25]. This is consistent with data from cannabis seizures in the UK, where high potency sinsemilla cannabis made up 15% of police seizures in 1999-2002[26], 50·6% in 2004–2005, 84·5% in 2007–2008, and 93·6% in 2016[19]. Trends towards high potency sinsemilla cannabis are reflected in seizure data in the US[8] and Australia[17], with average total THC content of 12% and 14% respectively, along with reductions in CBD content in the US[8]. Furthermore, figures from Washington State in the US show that concentrated cannabis extracts made up 21·2% of the market within two years of legal sales, suggesting a significant demand for extremely potent forms of cannabis[9]. Another notable change in legal cannabis markets has been the dramatic decrease in potency adjusted price over time (both at the retail and supply level)[9]. As price decreases, the price per unit of THC

also drops, and this might be expected to encourage purchasing behavior and increase exposure to THC[27]. Therefore, increased levels of harm might be attributed to a decline in the potency-adjusted price per unit of THC, and the increase in potency.. [8]

Why might adolescents be more susceptible to increases in cannabis potency?

Adolescence is a critical time for growth and development. This phase involves a distinct period of biological change, even beyond puberty, where a series of hormonal cascades lead to both cognitive and physical changes[28]. There is an expansion of the social self, an introduction to romantic and professional relationships, as well as an understanding of one's identity and role within contexts. Adolescence is marked by a period of dramatic cognitive development, where the brain undergoes neuronal maturation and cortical restructuring via processes of cortical thinning, synaptic reorganisation, and myelination of white matter tracts[29]. There are major changes in the PFC, hippocampus, amygdala, and the nucleus accumbens, areas which are responsible for harm avoidance, inhibition, decision making, learning and memory, emotion, motivation and reward[29]. While cortical functions are still under development, already developed reward related circuitry leads to the propensity for adolescents to seek novelty and reward in the face of uncertainty or potential negative outcomes, such as alcohol and illicit drugs[29]. The inability to control one's behavior, i.e. impulsivity, is often implicated in early onset adolescent drug use[30]. Behavioral inhibition tasks such as the Stop-Signal task (SST)[31] and the Go/No-Go task measure the ability (or inability) to suppress a task-induced response to a 'Go' stimulus. The results of neuroimaging and cognitive studies using SST and Go/No-Go tasks have revealed an association between impairment in neural responses on these tasks and the risk for adolescent substance use[32-34].

One such study concluded that adolescent cannabis users exerted greater neurocognitive effort, despite similar performance to adolescent non-cannabis users[35]. During the inhibition trials of a Go/No-Go task, cannabis users showed greater activation in the right dorsolateral prefrontal, bilateral medial frontal, bilateral inferior, superior parietal lobules, and right occipital gyrus compared to the comparison group. These brain regions are implicated in sustained attention[36], suggesting that users had to recruit more attentional resources in order to complete the tasks successfully. During the non-inhibitory trials, cannabis users showed greater activity in right prefrontal, insular and parietal cortices. Interestingly, abnormal activation of insular cortices has been found to be associated with a reduced awareness of internal and external cues, such as the ability to recognise ones' own substance use as problematic. It is therefore believed that abnormal activation of insular cortices plays a role in problematic substance use[37].

Behan et al.[32] also showed that adolescent cannabis users produced fewer successful inhibition trials in a Go/No-Go task compared to the non-cannabis users. Furthermore, a positive correlation between self-reported cannabis amount in the past week/month and parietal, bilateral cerebellar, and right frontal connectivity was shown, suggesting that the cerebellum is compensating when other task related regions are not engaged. While compensatory efforts have yielded similar results to controls in other studies[38], worse performances by cannabis users in Behan et al.[32] are consistent with the hypothesis that increased engagement of the cerebellum during response inhibition is associated with poorer task performance. Overall, the available literature suggests that cannabis users require additional neural resources to perform as well as non-users in cognitive inhibition tasks. In conclusion, and as illustrated in Fig. 2, adolescent developmental processes such as neuromaturation and predisposing factors such

as cognitive inhibition, impulsivity and reward sensitivity play a major role in the susceptibility of adolescents to the harmful effects of cannabis use. Whether these preceding risk factors influence the type of cannabis used is a question that has yet to be investigated.

The impact of cannabis potency on adolescent health

Epidemiological studies have consistently demonstrated that cannabis use in adolescence is associated with an increased risk of psychotic symptoms[39-43], anxiety[44] and in some cases depression[45]. The onset and magnitude of the effects of cannabis use on neurological function remains under debate. A recent review of longitudinal studies reported that early cannabis use was prospectively associated with neurocognitive decline particularly in IQ and episodic memory, with the greatest decline occurring in daily users[46]. However, almost all studies have categorised users according to frequency of cannabis use, and few studies have employed measures examining the impact of high versus low potency on either neurocognitive function or mental health outcomes. Morgan et al.[15] compared psychotic-like symptoms in 54 recreational cannabis users with 66 daily cannabis users aged 16-23 years. The results revealed lower psychotic symptoms in individuals with hair samples containing CBD compared with those without, however this effect was only seen in recreational users with high levels of THC in their hair. These findings suggest that CBD modulates the psychotic-like effects of THC, but that frequent users may be tolerant to these protective effects of CBD on THC harms. In a case control study of patients and controls aged between 18-65 years with first episode psychosis, Di Forti et al.[47] showed that compared to non-cannabis users, individuals who used skunk-like cannabis (high THC, minimal CBD) daily were more than 5-times as likely to be diagnosed with a psychotic disorder compared to non-cannabis users. Moreover, frequent use of high potency cannabis use was found to be associated with an increased risk

of relapse following first-episode psychosis[48]. These findings are consistent with experimental evidence suggesting that the psychotomimetic effects of THC are dose-dependent[13] and may be offset by CBD[14]. Overall, these studies clearly show the importance of highlighting the risk of high-potency cannabis products, particularly for adolescents who might be susceptible to the development of psychotic symptoms.

Few studies have accounted for cannabis type when assessing depression and anxiety in adolescent cannabis users. An anonymous global drug survey of young people (18> years) revealed that those with a lifetime diagnosis of depression and anxiety were significantly more likely to use high potency cannabis, in particular Butane Hash Oil (BHO)[49]. BHO is a cannabis extract that is frequently sold with high levels of THC, and relatively little CBD[20]. However, it must be noted that this study is cross-sectional and uses a lifetime diagnosis, which makes the existence and direction of causality difficult to establish[16]. A second cross-sectional study[15] had similar findings, with higher depression and anxiety scores reported in recreational and daily cannabis users (aged 16-23) with high levels of THC in hair samples, although this may have been attributable to increased levels of use and/or use of higher potency products.

A small number of studies have investigated the association between high and low potency cannabis and cannabis related problems. Freeman and Winstock[50] using the same data from the anonymous global drug survey revealed that young people reporting frequent use of high potency cannabis was associated with a greater severity of cannabis dependence. A 16-year study in the Netherlands[6] found an association between changes in THC concentrations in cannabis sold at national retail outlets and the number of people entering specialist drug treatment for cannabis problems. However, given that the majority of studies were cross-sectional, longitudinal studies are needed to investigate the existence and direction of potential causal relationships between cannabinoids and mental health outcomes in young people.

Cannabis use behaviours in adolescence

Whilst high potency cannabis is associated with greater harms compared to low potency cannabis in equal quantities what must be considered is whether cannabis users adjust (or 'titrate') their consumption according to THC/CBD levels. A handful of recent studies have explored such as possibility in young cannabis users[512-53]. Identified by a cluster analysis based on demographics, cannabis user and consumption characteristics, Korf et al.[51] found that the 'strongest high' group consisted mostly of younger participants (Mean age 22.65 yrs) who were least likely to report titration (reducing the number of grams used, depth of inhalation, or pace of smoking) in response to rising cannabis potency. Additionally, some members of this group actually reported using more cannabis as potency rose, further enhancing their exposure to THC. In a subsequent Dutch study assessing titration in an ecological setting, van der Pol et al.[52] discovered that THC concentration in users' own cannabis was positively correlated with the amount of cannabis they added to their joints. However, THC concentration was negatively correlated with inhalation volume, reducing THC exposure. Therefore, those who used higher potency cannabis tended to make larger joints, but partially engaged in titration by lowering their inhalation volume. The concept of partial titration was also supported by an ecological study of adolescent cannabis users (aged 16-24) in the UK[53]. That study found that as THC concentrations rose, users added less cannabis to their joints, partially reducing the effects of increased potency. However, they did not adjust their behavior according to concentrations of CBD in their cannabis. Measures of titration may also be important for identifying risk of transition to problematic use. A follow up of the Dutch study conducted by van der Pol et al. found that smoking topography while using cannabis (increased puff volume and duration) predicted the severity of cannabis dependence 1·5 years later after adjusting for baseline levels of dependence[52]. Taken together, these findings suggest that

cannabis users may partially (but not completely) adapt to changes in potency by titrating either the amount they add to their joints, and/or their inhalation. The contrasting effects of cannabis between adults and adolescents is further highlighted by Mokrysz et al.[54]. When measuring a range of acute effects following the inhalation of vaporized active or placebo cannabis, it was found that adolescent participants (16-17 years) felt less 'stoned' and experienced lower psychotic like symptoms and anxiety compared to adults (24-28 years). Furthermore, adults demonstrated a greater impairment in reaction time on spatial working memory and prose recall tasks. Moreover, where adults expressed satiety, adolescents did not, instead wanting more cannabis regardless of taking the active or placebo drug. It could therefore be suggested that the increased drive for the rewarding properties of cannabis is a possible contributing factor to escalating use in young people[54]. In conclusion, cannabis use behaviour, such as understanding cannabis potency, titration, satiety and acute cannabis effects, are important factors to consider when assessing the harms of cannabis use in adolescents. While future research must account for cannabis type, cannabis use behaviours also contribute to determining the amount of THC consumed by young people, and thus the potential harms they are exposed to.

Limitations

Even though evidence from several US states and countries report increases in cannabis potency, there are a number of limitations. Firstly, the majority of data is based on police seizures, which may result in sampling bias. However, there is no reason to believe that this sampling bias varies by time, so this is unlikely to account for the increases in potency observed in global cannabis markets. Moreover, data collected in the Netherlands confirmed a strong increase in potency from 2000 to 2004 in cannabis randomly sampled directly from

retail outlets[55]. Secondly, few cannabis potency studies address the issue of price, despite its important role in purchasing behavior and consumption and the possibility of contrasting trends in different regions or markets. pe Therefore in future studies, combining information on potency and price will be more informative than potency alone.

While clinical studies involving adult populations can be useful in drawing conclusions from the effects of cannabis use, it can be difficult to generalize these findings to adolescents in the community. Moreover, unmeasured confounding variables are a limitation common to many observational studies, and there is only limited evidence from placebo-controlled, double-blind studies[51]. For example, a major confound that is not adequately addressed in many studies to date is tobacco, which is frequently co-administered with cannabis, and has found to be associated with later incidents of psychosis[56]. Another major limitation that has been identified in this review is in relation to the measurement of cannabis use. Most studies evaluate the harms of cannabis use by employing duration and/or frequency, but neglect measures of cannabis potency or quantification of concentrations of THC and/or CBD. Self-reported data on potency may be limited by the wide range of THC and CBD concentrations within cannabis products. However, previous data has validated self-reported cannabis type against actual THC and CBD concentrations measured in the laboratory[53]. While laboratory tests are more precise, they are far less feasible for estimating long-term patterns of use (e.g. by repeatedly sampling an individual's cannabis use across the lifespan). We would therefore recommend that the assessment of cannabis potency should accompany questions about frequency and duration in healthcare and research settings. Pictorial aids (as illustrated in Figure 1) and verbal descriptions may be helpful for identifying different cannabis products. Moreover, researchers should use laboratory tests to calculate precise concentrations of THC and CBD in cannabis where possible. Unlike standard units of alcohol used in alcohol literature, there are currently no agreed standards for measuring cannabis[57]. The use of standardized cannabis use

units could vastly improve our understanding of variation in cannabis use and its consequences on adolescent health.

Future research

In light of the current research and its limitations, there are several avenues for future research. As there is a gap in the research focusing on adolescence, there is also an absence of cognitive and neuroimaging measures when focusing on potency[58]. While some studies have taken brain imaging measures from cannabis users, they have either been restricted to the limitations associated with hair analysis or have not included supplementary cognitive measures[59,60]. Studies employing these measures, alongside an accurate measure of cannabis potency, would allow for a better understanding of the neurocognitive effects across different cannabis products, both long and short-term.

With cannabis policy rapidly evolving, there is a possibility that further countries and states will legalise recreational cannabis use alongside existing US states and Canada. While it is important to recommend that age related restrictions for ultra-high potency products be guided by evidence based public health research it is acknowledged that the legal age of purchase is often based on the legal age of purchase of alcohol. Furthermore, while current legal frameworks in the US allow for legal cannabis potency and price to be set by the market, policy makers should consider the implementation of THC unit taxes, or THC thresholds[8]. For example, if harm increases as the price per unit of THC decreases, setting an acceptable level of tax per THC unit may help minimize harm. By contrast, if the potency of cannabis products is more important (irrespective of price) then setting an upper limit on THC concentration may be more effective. Furthermore, in order to fully evaluate the health consequences of changes in cannabis use it will be essential to determine the extent to which cannabis may act as a substitute or a complement to other drugs such as tobacco or alcohol[61.]

Conclusion

Given the growing body of research finding on cannabis potency and cannabis related harms, there is now a pressing need to understand how different types of cannabis products impact on adolescent health. Furthermore, a better understanding of the impact of cannabis use potency on adolescent neurocognition and mental health could inform future prevention programs (see Panel 1), policy decisions and clinical practice.

Panel 1: Cannabis prevention and information

With changes in policy potentially making cannabis increasingly accessible to adolescents in several states and countries worldwide, effective prevention and information is critical. Ap-

proximately half of all first-time cannabis use occurs before the age of 18[62], and with evidence suggesting that risk perception is more difficult to alter after first time use than before[63], it is important that adolescents are targeted at an early age (regardless of differential risk of use)[64]. Furthermore, a Cochrane review reported that although existing information and prevention programs have resulted in small reductions in drug use, the most effective programs have been those that involve a combination of drug information, social skills training (e.g. goal-setting and decision making), and anti-drug resistance skills training[65].

Programs must also be evidence-based, yet despite this, those that include information on potency or cannabis type are scarce. An internet delivered program, the Climate Schools, educated users on THC content. This program was efficacious in improving cannabis knowledge and reducing frequency of use[66]. Future prevention programs must allow for the discussion of how cannabis types differ in constituents, availability, risks, and harms so that adolescents are equipped with up-to-date evidence[67], allowing for the prevention or delay of cannabis use among adolescents most susceptible to its harmful effects.

Panel 2: Key messages

Problematic cannabis use typically peaks in adolescents 2-)an age group that may be particularly vulnerable to its harmful effects

Cannabis markets are dominated by high potency cannabis (high THC; low CBD), with THC content steadily increasing worldwide

Compared to low potency cannabis, high potency cannabis appears to be associated with a greater risk of psychotic symptoms, depression, anxiety and cannabis dependence

Adolescents only partially titrate their use of high potency cannabis, which can result in the consumption of high levels of THC.

Alongside more accurate measures of cannabis potency, further research must adopt longitudinal, cognitive, and neuroimaging measures to gain a better understanding of the effects of adolescent cannabis use

With cannabis policy rapidly changing, up-to-date evidence should inform decisions on potency taxes or potency thresholds, as well as legal age of purchase

Authors' contributions

CM had the idea for this paper. JW conducted the literature search and wrote the initial draft. All authors contributed to the writing and editing of the paper. All authors agreed the final version.

Declaration of interests

All authors declare no competing interests.

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Search strategy and selection criteria

The current literature review originated from a comprehensive search of the literature via PubMed, Google Scholar, and the author's own files. The search involved key terms such as 'adolescence', 'cannabis', 'early-onset cannabis use', 'cannabis potency', 'cannabis harms', and 'delta-9-tetrahydrocannabiol, THC: Cannabidiol, CBD'. As research focusing on adolescent cannabis use is scarce, the current review included English written articles published in the last 15 years (January 2003), with the exception of original citations for measurements (e.g. Stop-Signal task). Finally, the decision to include articles was based on the relevance within the scope of this review.

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