POTENTIAL FOR ABUSE

In 21 U.S.C. 802, the Controlled Substances Act refers to "potential for abuse" as a factor used for the scheduling of drugs but does not provide a clear definition of this term. The Food and Drug Administration (FDA) offers the following definition: "Drug abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Therefore, abuse potential refers to the likelihood that abuse will occur with a particular drug product or substance with CNS [Central Nervous System] activity" (FDA, 2017). To examine the potential for abuse, it is useful to distinguish between acute (short-term) and chronic (long-term) effects cannabis may have on human health.

Acute Effects

Most of the research conducted on the acute impact that cannabis may have on human health has focused on delta-9-tetrahydrocannabinol (THC). Recent studies on the acute impact of cannabidiol (CBD) on human health suggested no significant cognitive or psychomotor impairment (Spindle et al., 2020; Drennan et al., 2021; Lo et al., 2024).

Overall, the risk of death due to cannabis overdose is extremely low compared to the risks of opioid and stimulant drug overdoses (WHO, 2016; Rock et al., 2022). Nevertheless, cannabis can produce a range of acute effects depending on the dose used, including enhanced sensitivity to colors and/or music, altered perception of time, decrease in short-term memory, euphoria, attention deficits, and tachycardia (Lawn et al., 2023), although the most robust effects were reported for verbal learning and working memory (Wickens et al., 2022).

There is a wide variation in how individuals are affected by cannabis (Lawn et al., 2023), and acute cannabis intoxication may occur to both naïve and chronic users. The route of administration affects the onset of symptoms, which may take longer after ingesting cannabis (2–3 hours) than after inhaling or smoking cannabis (15–30 minutes), with the symptoms after ingesting cannabis lasting longer than after inhaling cannabis (Kluemper, 2022; Bridgeman & Abazia, 2017; NASEM, 2017).

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Although the risk of acute toxicity of cannabis is relatively low, there have been reports of fatalities caused by brain infarction among teenagers after acute use of the drug (Crippa et al., 2012). Also, concern has arisen over cannabis overdose incidents among children who mistakenly ingested edible cannabis (Crippa et al., 2012; Wong & Baum, 2019; Noble et al., 2019).

Chronic Effects

Most research conducted on the long-term impact of cannabis on human health has focused on THC. Daily consumption of cannabis (THC in particular) can develop dependence, producing persistent, chronic impairments in memory and cognition, particularly when cannabis use begins in adolescence (WHO, 2016; NASEM, 2017). The following factors have been associated with progression to dependence:

- *Potency*: The consumption of high-potency cannabis, which has on average doubled worldwide over recent decades, has been associated with adverse psychological outcomes and dependence (Englund et al., 2017; Smart et al., 2017; Petrilli et al., 2023; Schlag et al., 2021; NASEM, 2017; Hall & Lynskey, 2020; WHO, 2016)
- *THC:CBD ratio*: Related to potency, cannabis with a relatively low THC:CBD ratio may be less likely to have adverse effects than cannabis with a high THC:CBD ratio; however, the evidence on this topic is mixed (Englund et al., 2023; Pintori et al., 2023; Solowij et al., 2019).
- *Heavy use and early onset*: There is stronger evidence that the risk of cannabis dependence increases with heavy amounts consumed, high- frequency use (heavy, daily), and early onset of use (starting in adolescence) (Schlag et al., 2021) (NASEM, 2017). However, strength of these findings has been questioned, as research often ignores potentially confounding factors such as polysubstance abuse (Pintori et al., 2023).
- *Co-morbid presence of various psychological and mental health factors*: Cannabis dependence tends to occur more often among individuals who report any lifetime psychiatric, mood, anxiety, conduct, and/or personality disorder, including low self-esteem, low self-control, and attention deficit hyperactivity disorder (ADHD) (Hall & Lynskey, 2020; WHO, 2016; Schlag et al., 2021; NASEM, 2017).
- *Flavored products*: Flavored cannabis is becoming increasingly popular in the U.S. (Watkins et al., 2023; Chaffee et al., 2023), and it has been posited that flavors of inhaled cannabis products may have an effect similar to inhaled tobacco in terms of initiation or dependence (Watkins et al., 2023). However, evidence for such an association is unclear (Glasser et al., 2022).

- *Cannabis as a gateway drug*: Polysubstance use is common among cannabis users, in particular those who use alcohol (Hasin & Walsh, 2020; Gorfinkel et al., 2021; De Aquino et al., 2019). Almost 50 years ago cannabis was proposed to be a "gateway drug" for alcohol, tobacco, and other illicit drugs (Kandel, 1975). Recent reviews, however, found no evidence to support such a hypothesis (Sabia et al., 2021; Jorgensen & Wells, 2021; NASEM, 2017), and some studies even hypothesized that cannabis use can protect against the onset of tobacco and/or alcohol use (Cho et al., 2021; Cohn & Elmasry, 2023); however, this hypothesis has not been substantiated (Cohn & Elmasry, 2023).

Frequent use of cannabis may lead to tolerance (i.e., the need for higher doses to achieve a therapeutic effect over time) of the impairing effects of THC on some (or all) cognition and psychomotor functions, albeit not all frequent cannabis users develop tolerance (Ansell et al., 2023; Colizzi & Bhattacharyya, 2018). Recent work has shown that women can develop tolerance for the pain-relieving effects of THC more readily than men (Piscura et al., 2023; Matheson & Le Foll, 2023; Cooper & Craft, 2018). The few studies that looked at repeated CBD administration do not report development of tolerance (Kluemper, 2022).

A T-break ("tolerance break") has been proposed as a strategy for managing cannabis use, but there is a dearth of scientific research on the topic. A T-break generally involves a self-directed process of abstaining from cannabis for a predetermined amount of time without the desire to quit, with the primary goal of reducing tolerance levels so that a smaller amount of cannabis will be needed to achieve the same high (Fontana et al., 2022; Ansell et al., 2023). A recent review of websites serving cannabis users found that the recommended length of T-breaks varies from 2 to 4 weeks, although no sound scientific basis exists for these durations (Ansell et al., 2023). Furthermore, taking a T-break may be a marker of increased risk for problematic outcomes for some cannabis users (Ansell et al., 2023).

Potential for Abuse Among Population Subgroups

- *Racial/ethnic minorities*: There are differences in the prevalence of self-reported cannabis use in the U.S. across racial/ethnic groups, with Black Americans having the highest rate of cannabis use (10.7%), followed closely by non-Hispanic whites (8.4%) and Hispanics (7.2%) (NASEM, 2017). Despite differences in prevalence, research is unclear on whether cannabis-related risk and/or the presence of protective factors vary across racial/ethnic groups (Stoa, 2022; Rafei et al., 2023).

- *Older adults*: Following the legalization of cannabis (Wolfe et al., 2023), there has been an increase in its use among individuals ages 50+, mainly due to a combination of medical and quasi-medical reasons (Hall & Lynskey, 2020). Although cannabis use may help individuals with medical problems (e.g., to assist with sleep, control pain, stimulate appetite), compared with younger individuals, older users may run a higher risk of experiencing adverse health effects, such as confusion, dizziness, and delirium, increasing the risk of falls and motor vehicle crashes. As a result, the benefit/risk ratio cannabis poses for older users remains unclear (Hall & Lynskey, 2020; Riggs & Thant, 2022).
- *Sex*: Compared with males, there is an association between females and the reinforcing and/or rewarding effects of cannabis at lower doses, which in combination with a faster development of tolerance could lead to rapid escalation of cannabis problems among females (Matheson & Le Foll, 2023). That said, sex-related biological influences on the responses to cannabis are still not fully understood (Matheson & Le Foll, 2023; Cooper & Craft, 2018).

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