FOUNDATION FOR TRAFFIC SAFETY

PHARMACOLOGY

CANNABIS FACT SHEET | DEC 2024

Pharmacology studies how a drug interacts with the body and how the body interacts with the drug. In other words, it studies how drugs get into the body, what they do in the body, how they do it, and the ways in which the body breaks down and gets rid of them. (Canadian Centre on Substance Use and Addiction, 2017).

DOWNLOAD THE FULL REPORT

About Cannabis and Cannabinoids

The three most recognized species of the genus Cannabis are: Cannabis sativa, Cannabis ruderalis, and Cannabis indica. However, as a result of interbreeding, it has been suggested that only a single species of cannabis should be recognized: Cannabis sativa (Schilling et al., 2020). There are more than 100 different compounds called cannabinoids, including delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN). Cannabinoids can be synthesized by the cannabis plant (called phytocannabinoids), as well as by the human body (endocannabinoids), or prepared in the laboratory (synthetic cannabinoids).

Suggested Citation

Romano, E., Romosz, A., Taylor, E., Murphy, J., Thomas, S., Moore, C., & McKnight, S. (2024). *Cannabis Use, Public Health, and Traffic Safety: Outcomes from the Scientific Literature and Expert Opinion on the Potential Impacts of Rescheduling* (Technical Report). Washington, D.C.: AAA Foundation for Traffic Safety.

Cannabinoids and the Human Body

Cannabinoids act primarily through action on the endogenous cannabinoid system (ECS): a vast network of chemical signals and cellular receptors located throughout the human brain and body. The ECS regulates many critical human tasks and functions such as learning, memory, emotional processing, sleep, pain control, and immune responses (Piscura et al., 2023; Bridgeman & Abazia, 2017).

Two of these receptors are particularly relevant to the metabolism of cannabis: CB1 and CB2. CB1 receptors are primarily located in the human brain, largely concentrated in regions involved in memory, emotional responses, cognition, motivation, and motor coordination (Piscura et al., 2023; WHO, 2016). CB2 receptors are found primarily in the human body, playing a role in the regulation of the immune system and acting on the gastrointestinal tract, liver, heart, muscle, skin, and reproductive organs (WHO, 2016).

THC is the main cannabinoid with psychoactive properties. THC binds to the CB1 receptor to exert its psychoactive effect.

Unlike THC, CBD has a low affinity for the CB1 receptor. Further, CBD appears to slow or inhibit the binding of THC components to CB1. As such, CBD does not produce acute intoxication, has been proven to treat refractory epileptic syndromes in children, and may have anti-inflammatory, anxiolytic, and antipsychotic indications (Bridgeman & Abazia, 2017; Pennypacker et al., 2022).

Originally developed as research tools aimed to investigate the endogenous cannabinoid system and to develop clinical therapies, the majority of Synthetic Cannabinoid Receptor Agonists (SCRAs) are highly potent, with elevated binding affinity with the CB1 receptor.

Routes of Administration

The route by which cannabis is used can impact the drug's onset, intensity, addictive potential, and negative consequences (Bridgeman & Abazia, 2017; Kluemper, 2022).

Smoking

Overall, smoked cannabis tends to produce greater, more immediate effects than edibles. After inhalation, THC is rapidly transferred from the lungs to the blood during smoking, which causes the effects of smoking cannabis to reach their maximum 6 to 30 minutes after inhalation, disappearing within 2 to 3 hours (Chayasirisobhon, 2020; Bridgeman & Abazia, 2017). However, there is important variation in these responses, caused by variations in factors such as duration of intake, inhalation volume, and the inhalation device (Preteroti et al., 2023).

Vaping

Vaporization tends to provide effects similar to smoking, but with a reduced exposure to the byproducts of combustion. As such, it was suggested that compared with smoking cannabis, vaping may have some benefits (Bridgeman & Abazia, 2017; Fischer et al., 2022; Preteroti et al., 2023). However, research on this possibility is lacking. Little is known about the long-term impact of vaporized cannabis on the respiratory system and the possibility of the downstream development of lung diseases (Preteroti et al., 2023).

Oral Ingestion

Orally ingested cannabis passes first through the liver, which compared to inhalation, reduces the amount of cannabis needed to produce a response (i.e., ingested cannabis has a lower "effective dose" than inhaled cannabis) (Kluemper, 2022).

In the liver, THC is metabolizes into 11-OH-THC (psychoactive) and then into 11-COOH-THC (not psychoactive), or is eliminated. Although 11-OH-THC can also be formed after consumption of THC from inhalation (vaping, smoking), levels of 11-hydroxy-THC are typically higher when cannabis is eaten rather than inhaled (Huestis et al., 1992).

Following oral ingestion, psychotropic effects manifest within 30 to 90 minutes, reach their maximum effect after 2 to 3 hours, and last for about 4 to 12 hours, depending on the dose (Bridgeman & Abazia, 2017; Okey, 2023; Kluemper, 2022). Thus, compared with inhaled cannabis, edible cannabis has a slower onset of effects, but often has a longer lasting "high" effect.

Distribution, Accumulation, and Half-Life

THC and CBD have a half-life (i.e., the time required for the concentration of the drug to reach half of its original value) that is biphasic. That is, the curve that the drug concentration follows presents two separate parts: a steep portion and a shallow portion of the curve (Preteroti et al., 2023).

After being absorbed, cannabinoids spread to less vascularized tissues (e.g., adipose tissue) where they accumulate and are subsequently released. The release of cannabinoids from adipose tissue can take place for weeks after consumption (Preteroti et al., 2023; Kluemper, 2022).

Regarding cannabis half-life, THC has an initial and brief half-life of 4 hours (the steep part of the curve), and a terminal half-life (the shallow and longer part of the curve) of 25–36 hours. CBD has an initial half-life of 1–2 hours and a terminal half-life of 18–32 hours (Preteroti et al., 2023).

Cannabinoids and their metabolites eventually are eliminated in the urine and feces, a process that can be prolonged due to the highly lipophilic nature of cannabinoids (Kluemper, 2022). Chronic users redistribute inactive metabolites from adipose tissue into the blood and urine, which is the underlying reason why urine drug screens yield positive results weeks after cannabis was last used (Kluemper, 2022).

Cannabis Used in Conjunction with Alcohol

Both cannabis and alcohol have been shown to interact through the endogenous cannabinoid system (ECS), although alcohol can also act on a variety of neurochemical processes (Wolfe et al., 2022).

Cannabinoids can be involved with the rewarding effects of alcohol being more reinforcing at lower alcohol doses than at higher doses. There is substantial evidence that, compared to the single use of either substance, the simultaneous use of alcohol and cannabis increases impairment on a number of behavioral and neurocognitive tasks (Gunn et al., 2022).

Despite the noted psychoactive toxicity of the combined use of alcohol and cannabis, some researchers have recently posited that cannabis could be used as a substitute for alcohol in treatments for Alcohol Use Disorders. However, research on this possibility is lacking (Wolfe et al., 2022; Gendy et al., 2023; Gunn et al., 2022).

Cannabis Used in Conjunction with Tobacco

Very little is known about the pharmacology of combined use of nicotine and cannabis. Tobacco smoking has been associated with lower CB1 receptor levels, which suggests that tobacco smokers may be less sensitive to the effects of THC (Nasrin et al., 2023; Hindley et al., 2020).Indeed, recent research showed that CBD and its active metabolite have an inhibitory effect on nicotine (Nasrin et al., 2023).

Although research suggests cannabis and tobacco could each be used to counter the effects of the other, much research is needed before any therapeutic recommendation can be formulated (Hindley et al., 2020).

References

Bridgeman M.B., & Abazia D.T. (2017). Medicinal cannabis: history, pharmacology, and implications for the acute care setting. Pharmacy and therapeutics, 42(3), 180–188. https://pmc.ncbi.nlm.nih.gov/articles/PMC5312634/

Canadian Centre on Substance Use and Addiction. (2017). Pharmacology and Substance Use. Available at: https://www.ccsa.ca/sites/default/files/2019-04/CCSA-Pharmacology-Substance-Use-Summary-2017-en.pdf.

Chayasirisobhon S. (2020). Mechanisms of Action and Pharmacokinetics of Cannabis. The Permanente Journal, 25, 1–3. https://doi.org/10.7812/tpp/19.200
Fischer B., Robinson T., Bullen C., Curran V., Jutras-Aswad D., Medina-Mora M.E., Pacula R.L., Rehm J., Room R., van den Brink W., & Hall W. (2022). Lower-Risk Cannabis Use Guidelines (LRCUG) for reducing health harms from non-medical cannabis use: A comprehensive evidence and recommendations update. International Journal of Drug Policy, 99, 103381. https://doi.org/10.1016/j.drugpo.2021.103381

Gendy M.N., Frey B.N., Van Ameringen M., Kuhathasan N., & MacKillop J. (2023). Cannabidiol as a candidate pharmacotherapy for sleep disturbance in alcohol use disorder. Alcohol and Alcoholism, 58(4), 337–345. https://doi.org/10.1093/alcalc/agad031

Gunn R.L., Aston E.R., Metrik J. (2022). Patterns of cannabis and alcohol co-use: Substitution versus complementary effects. Alcohol Research: Current Reviews 42(1). https://doi.org/10.35946/arcr.v42.1.04

Hindley G., Beck K., Borgan F., Ginestet C.E., McCutcheon R., Kleinloog D., Ganesh S., Radhakrishnan R., D'Souza D.C., & Howes O.D. (2020). Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. The Lancet Psychiatry, 7(4), 344–353. https://doi.org/10.1016/s2215-0366(20)30074-2

Huestis M.A., Henningfield J.E., & Cone E.J. (1992). Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. Journal of Analytical Toxicology, 16(5), 276–282. https://doi.org/10.1093/jat/16.5.276

Kluemper A. (2022). Clinical Pharmacology of Cannabinoids. In Riggs P., & Thant T. (Eds.), Cannabis in Psychiatric Practice: A Practical Guide. Psychiatry Update, vol 3. (13-26). Springer. https://doi.org/10.1007/978-3-031-04874-6_2

Nasrin S., Coates S., Bardhi K., Watson C., Muscat J.E., & Lazarus P. (2023). Inhibition of Nicotine Metabolism by Cannabidiol (CBD) and 7-Hydroxycannabidiol (7-OH-CBD). Chemical research in toxicology, 36(2), 177–187. https://doi.org/10.1021/acs.chemrestox.2c00259

Okey S. (2023). How High are You? An EMA Comparison of Subjective Effects After Edible and Smoked Cannabis, in Series How High are You? An EMA Comparison of Subjective Effects After Edible and Smoked Cannabis. [PhD Thesis, Arizona State University]. https://hdl.handle.net/2286/R.2.N.187682

Pennypacker S.D., Cunnane K., Cash M.C., & Romero-Sandoval E.A. (2022). Potency and Therapeutic THC and CBD Ratios: U.S. Cannabis Markets Overshoot. Frontiers in Pharmacology, 13, 921493. https://doi.org/10.3389/fphar.2022.921493

Piscura MK., Henderson-Redmond A.N., Barnes R.C., Mitra S., Guindon J., & Morgan D.J. (2023). Mechanisms of cannabinoid tolerance. Biochemical Pharmacology, 214, 115665. https://doi.org/10.1016/j.bcp.2023.115665

Preteroti M., Wilson E.T., Eidelman D.H., & Baglole C.J. (2023). Modulation of pulmonary immune function by inhaled cannabis products and consequences for lung disease. Respiratory Research, 24(1), 95. https://doi.org/10.1186/s12931-023-02399-1

Schilling S., Melzer R., & McCabe P. F. (2020). Cannabis sativa. Current biology : CB, 30(1), R8–R9. https://doi.org/10.1016/j.cub.2019.10.039WHO. (2016). The health and social effects of nonmedical cannabis use. World Health Organization.

Wolfe S.A., Vozella V., & Roberto M. (2022). The synaptic interactions of alcohol and the endogenous cannabinoid system. Alcohol research: current reviews, 42(1). https://doi.org/10.35946/arcr.v42.1.03