FLOW HIJACKED

CANNABIS

Molecule, Mind, Development, and the Nonlinear Brain

A scientific lecture-monograph

Endocannabinoid signaling • developmental vulnerability • cognition • psychosis • addiction • physical health • therapeutics • state space

“Precision is not coldness. It is the refusal to exaggerate a risk, erase a benefit, hide a limitation, or abandon a person inside a slogan.”

Evidence reviewed through 4 September 2026

216-source frozen core • 116-claim evidence ledger • 16 original scientific figures

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Preface: holding several truths at once Back to TOC

Cannabis is unusually good at defeating simple sentences. “Cannabis is safe” is false as a general statement. “Cannabis is dangerous” is too coarse to guide anyone. “Cannabis is medicine” confuses a plant with several molecules, formulations, doses, indications, and standards of evidence. “Cannabis causes schizophrenia” turns a probabilistic contribution into a universal mechanism. “Cannabis has nothing to do with schizophrenia” ignores experimental effects, dose-response evidence, and the repeated observation that risk is concentrated in frequent, high-THC exposure. “The brain finishes developing at twenty-five” compresses a long, heterogeneous developmental landscape into a birthday.

This book is built to resist those compressions. Its central scientific claim is not that cannabis is uniquely evil or uniquely benign. It is that **cannabis is not one exposure**, and that trajectories depend on the interaction of product chemistry, delivered dose, route, frequency, developmental timing, prior learning, genetics, psychiatric vulnerability, sleep, stress, other substances, and environment. Modern high-THC products make the word *cannabis* less informative than it once was. A low-THC, CBD-rich oral medicine used under clinical monitoring and a high-potency concentrate used repeatedly by a sleep-deprived sixteen-year-old are not two versions of the same scientific event.

The human meaning matters alongside the pharmacology. People use cannabis for pleasure, curiosity, music, ritual, appetite, social belonging, pain, panic, insomnia, trauma, loneliness, and relief from an inner life that feels too loud. Some use occasionally without serious consequence. Some discover a medicine. Some experience fear or psychosis after one exposure. Some slowly organize their evenings, relationships, and sense of self around a substance that once seemed to make life easier. Understanding mechanism should enlarge compassion. It should never turn a person into a receptor diagram.

The work is deliberately weighted toward harms, developmental vulnerability, addiction, and psychiatric risk because those topics are often minimized by the language of “natural,” “wellness,” or legalization. It also includes a rigorous therapeutic section because denying genuine benefits would be just as unscientific. Pharmaceutical cannabidiol is an effective antiseizure medicine for particular syndromes. Certain standardized THC-containing products have modest evidence for chemotherapy-related nausea, multiple-sclerosis spasticity, and some chronic pain. Those facts do not certify every cannabinoid, retail product, route, or claim.

This is educational material, not personal medical advice. Severe confusion, chest pain, loss of consciousness, persistent vomiting, suicidal intent, or psychotic symptoms require urgent professional assessment. A person who is pregnant, breastfeeding, taking prescription medication, living with a heart condition, or concerned about dependence deserves individualized clinical care rather than a generic internet rule.

The intellectual question Back to TOC

What happens when an exogenous chemical signal enters a regulatory system whose normal job is to tune synapses, appetite, stress, pain, memory, reward, and development—and what determines whether the resulting trajectory is transient pleasure, useful symptom relief, functional impairment, dependence, or psychiatric destabilization?

The governing answer is conditional. Δ9-tetrahydrocannabinol, or THC, can perturb a widely distributed endocannabinoid control system. The perturbation is not applied to an empty brain. It lands in a living, adaptive system with a history. The same nominal dose can therefore produce different brain concentrations, expectations, sensations, behaviors, and learning. Repetition changes the receiving system. Context changes what is learned. Development changes which functions are being refined. Vulnerability changes how close the system may already be to an unstable transition.

The Flow Hijacked lens enters here. It treats the brain as a nonlinear, metastable, adaptive system that moves among transient states rather than as a static collection of parts. It asks how reinforcement deepens some paths, how cues acquire salience, how short-term relief can alter future predictions, and why a perturbation that is absorbed in one person can push another across a threshold. This lens is a scientific synthesis, not a discovered cannabis-specific mechanism. Whenever it extends beyond established evidence, the text says so.

How evidence is spoken in this book Back to TOC

“Well established” is reserved for findings supported by direct, reproducible evidence, such as acute THC-related impairment or the clinical efficacy of pharmaceutical CBD in named epilepsy syndromes. “Supported by convergent evidence” means that several designs point in the same direction. “Probable causal contribution” means that temporal order, dose-response, experiment, mechanism, and triangulation collectively support causality while leaving uncertainty about magnitude and individual attribution. “Associated with” means just that. “Mechanistically plausible” identifies a bridge from molecular or preclinical evidence that has not been established as the human clinical route. “Preclinical” means that cells or animals—not human patients—carry the evidential weight. “Flow Hijacked synthesis” and “new hypothesis” are marked explicitly.

No observational adjustment makes measured confounding disappear. Tobacco, alcohol, stimulants and other drugs; childhood adversity; family psychiatric liability; socioeconomic conditions; educational disengagement; risk-taking; sleep disruption; pre-existing symptoms; and reverse causality recur because they genuinely matter. Uncertainty is not used as a sedative, however. A literature can remain imperfect while still becoming strong enough to justify caution.

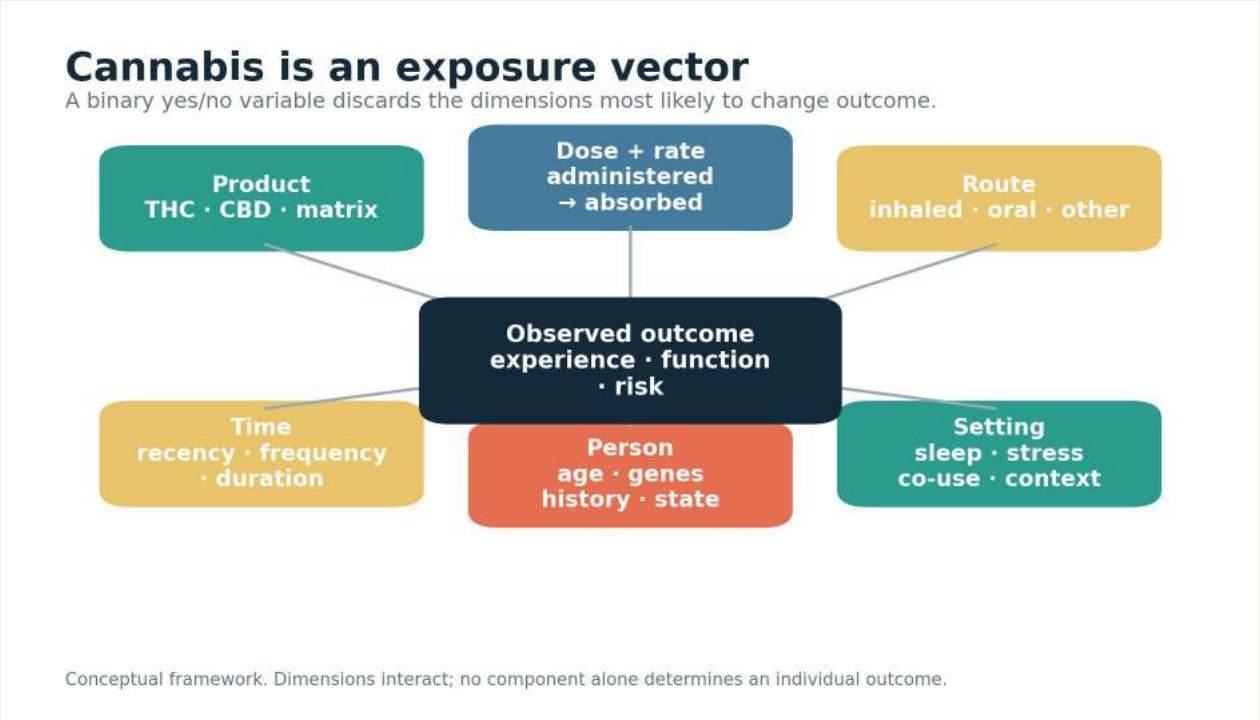

Figure 1. Cannabis as an exposure vector rather than a binary. Product chemistry, delivered dose, route, frequency, timing, person-level vulnerability, and setting jointly define the event. The same label—"cannabis use"—can hide orders-of-magnitude differences in exposure.

Part I — What cannabis actually is Back to TOC

1. From a flowering plant to a family of exposures Back to TOC

The plant is real; the categories are negotiated

Cannabis is a genus of flowering plants in the family Cannabaceae. Its taxonomy has been argued over for centuries: one highly variable species, *Cannabis sativa*, or multiple species and subspecies, commonly including *sativa*, *indica*, and sometimes *ruderalis*. The dispute is not merely botanical. Humans have moved, selected, crossed, and clonally propagated cannabis for fiber, seed, resin, medicine, and intoxication. Modern commercial breeding has produced extensive admixture. A retail name may descend from a lineage story, a breeder's label, a sensory association, or a marketing decision. It is not a genome sequence.

The plant is usually dioecious—male and female flowers occur on different individuals—although monoecious forms exist and cultivation practices can alter expression. Drug-type production favors unfertilized female inflorescences because glandular trichomes on bracts and nearby tissues accumulate resin rich in cannabinoids and volatile compounds. The word *flower* in a shop therefore does not refer to an inert dried leaf. It usually refers to dried, resin-bearing inflorescence whose chemical composition has been shaped by genotype, growing conditions, harvest timing, curing, storage, and processing.

Plant taxonomies answer questions about ancestry and morphology. A clinical exposure taxonomy asks different questions: Which cannabinoids are present? In what concentrations? In what chemical forms? How much reaches the circulation and brain? Over what time course? Which other compounds are co-delivered? Those are not interchangeable classification systems.

Why “indica” and “sativa” fail as dosing instructions

Retail culture often maps *sativa* to stimulation and creativity, *indica* to sedation and “body effects,” and *hybrid* to a predictable mixture. That scheme can feel validated because expectations, product choice, aroma, dose, and social setting influence experience. But chemical and genetic surveys repeatedly find that commercial names and indica–sativa labels do not reliably partition products into stable biological groups. Samples sold under the same name can differ meaningfully; differently named samples can overlap. Terpene synthase variation explains some aroma diversity, yet the label still does not tell a consumer the delivered THC dose or predict a particular mental state (Watts et al., 2021; Smith et al., 2022).

This does not mean that all products are alike. It means that the popular labels are low-resolution proxies. A chemovar—a chemically characterized variety—is more informative when it reports at least THC, CBD, and major constituents. Even then, a certificate of analysis is not a destiny. Two people can inhale the same verified material and experience different effects; the same person can respond differently on a calm afternoon and after two nights of poor sleep.

The useful corrective is not a new rigid taxonomy. It is a hierarchy of questions. First ask about the major cannabinoids and their concentrations. Then ask about amount and route. Then frequency, age, tolerance, and co-use. Then ask who the person is and what state they are in. “Indica or sativa?” comes much later, if it belongs at all.

Flower, hashish, resin, oils, and concentrates

Dried flower is plant material, commonly ground and combusted or heated in a vaporizer. Hashish is a concentrated preparation of mechanically collected or otherwise separated resin glands, traditionally pressed into a solid. Hash oil is an extract in which cannabinoids and other lipophilic constituents have been concentrated into an oil or viscous resin. Modern concentrates include products described as wax, shatter, budder, rosin, distillate, and live resin. The names partly describe texture or manufacturing history; they do not ensure a stable pharmacological profile.

Extraction can change far more than concentration. A distillate may contain very high THC with a narrower volatile profile. A "full-spectrum" extract may retain more compounds, though that phrase has no universal clinical meaning. Solventless does not mean riskless. A concentrate can deliver a large amount of THC in a small mass, allowing rapid administration and reducing the sensory cues that once placed a practical ceiling on dose. The scientific distinction is not nostalgia for old cannabis. It is exposure geometry: concentration, bolus size, rate of delivery, and repetition.

An edible places cannabinoids in food, drink, capsule, lozenge, or confectionery. The route transforms the event. Oral THC must cross the gastrointestinal tract and liver before systemic circulation, producing delayed and variable exposure and more 11-hydroxy-THC. A person who expects an inhalation-like onset may mistakenly conclude that nothing has happened while the dose is still being absorbed. Attractive formats and imperfect storage also create a pediatric poisoning risk. These are pharmacokinetic and product-design hazards, not moral facts about the person who bought the product (NASEM, 2024).

Oils may be swallowed, held in the mouth, or delivered through metered oromucosal products. "Sublingual" consumer use often combines mucosal and swallowed exposure; contact time and formulation matter. Topicals are designed for local application, but labels such as "transdermal" imply systemic delivery that many products have not demonstrated. Pharmaceutical formulations include purified cannabidiol oral solution, synthetic or plant-derived THC analogues such as dronabinol, the synthetic cannabinoid nabilone, and standardized approximately 1:1 THC:CBD oromucosal spray such as nabiximols. Each is a distinct intervention.

Cannabis is not one drug

Calling cannabis "one drug" is like calling a pharmacy shelf "one treatment," though the analogy is imperfect because cannabis constituents co-occur in variable matrices. At minimum, a scientifically useful exposure record needs product type, route, estimated THC and CBD dose, frequency, recency, duration, age of initiation, and whether use occurs with tobacco, alcohol, or other substances. Potency alone is not dose. A product labeled 80 percent THC tells us the fraction by mass, not how much was delivered, inhaled, absorbed, or reached the brain. Frequency alone is not cumulative exposure. "Ever used" and "daily high-potency use" should never be collapsed without a compelling analytic reason.

One practical representation is an exposure vector:

$$x = (\text{THC}, \text{CBD}, \text{other constituents}, \text{dose}, \text{route}, \text{rate}, \text{frequency}, \text{duration}, \text{developmental time}, \text{co-exposures}, \text{context}).$$

Two observations that both receive the value "1" in a binary cannabis variable may be distant in this state space. Much of the apparent conflict in cannabis research begins with the loss of that information.

The social product

A cannabis product is also a social object. Packaging can imply medicine, craft, rebellion, luxury, wellness, or candy. Legalization can improve testing and remove criminal penalties while also enabling commercialization, product innovation, and normalization. Illicit prohibition can add contaminants and violence while making product composition unknowable. These truths can coexist. Public-health analysis has to separate the pharmacology of cannabinoids from the effects of regulation, marketing, policing, inequality, and access to care (NASEM, 2024).

That separation also protects people from stigma. A respiratory hazard from combustion is not an argument about criminal law. A psychosis warning is not a judgment about character. A benefit from a standardized medicine is not an endorsement of a retail industry. Science becomes clearer when one question is not forced to answer all the others.

2. A chemistry of signals, precursors, and uncertainty Back to TOC

Where cannabinoids come from

The plant does not chiefly synthesize neutral THC and CBD in the forms familiar from product labels. It synthesizes acidic precursors. A shared biosynthetic branch gives rise to cannabigerolic acid, CBGA, which enzymes can convert toward tetrahydrocannabinolic acid, THCA; cannabidiolic acid, CBDA; and cannabichromenic acid, CBCA. Genetics in cannabinoid synthase regions strongly influences which branch dominates. Environment and processing then modify the measured profile.

THCA is not simply “inactive THC.” It has its own poorly characterized pharmacology and limited human evidence, but it is far less intoxicating at usual exposures because it does not readily produce the same central CB1 effect. Heat removes a carboxyl group as carbon dioxide—a reaction called decarboxylation:

$$\mathrm{THCA} \rightarrow \Delta 9\text{-THC} + \mathrm{CO_2}$$

$$\mathrm{CBDA} \rightarrow \mathrm{CBD} + \mathrm{CO_2}$$

Time and storage can also drive transformation. Further oxidation and degradation can convert THC toward cannabinol, CBN. CBN is *cannabinol*, not cannabidiol. This matters because a single missing syllable can turn one molecule into another.

The formulas do not reveal pharmacology. THC and CBD share the molecular formula $C_{21}H_{30}O_2$ but differ in structure. That difference changes receptor interaction, conformation, metabolism, and behavioral effect. Molecular similarity is not functional equivalence.

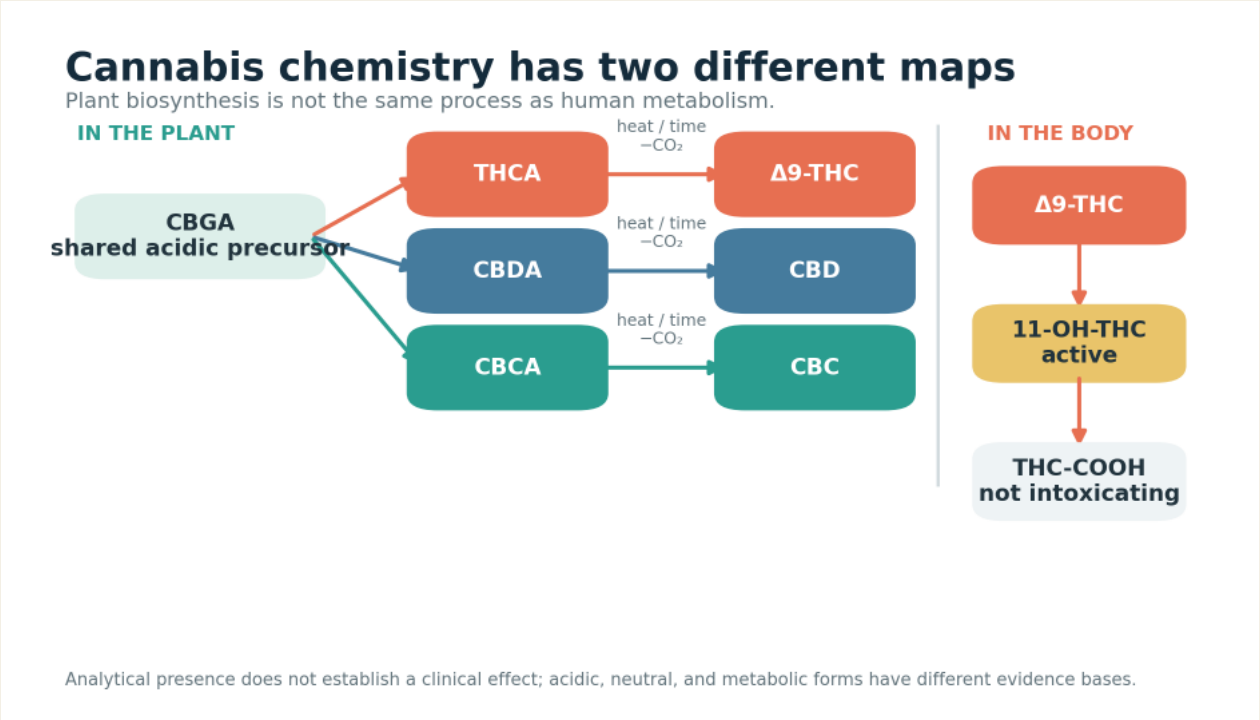

Figure 2. Cannabis chemistry map. CBGA branches toward acidic cannabinoids; heat promotes decarboxylation; THC undergoes hepatic oxidation to active 11-OH-THC and then largely inactive THC-COOH. The map distinguishes plant biosynthesis from human metabolism.

Δ9-THC: the principal intoxicant

Δ9-THC is the dominant intoxicating phytocannabinoid in most modern drug-type cannabis. It acts as a partial agonist at CB1 and CB2 receptors. “Partial” does not mean trivial. Effect depends on ligand efficacy, receptor density, receptor reserve, cell type, endogenous tone, and network position. CB1 is extraordinarily abundant in the brain. Exogenous THC also arrives with a spatial and temporal pattern unlike the brief, locally synthesized endocannabinoid signals it imitates.

Acute effects can include euphoria, altered time perception, intensified sensory salience, relaxation, laughter, appetite, and pain modulation. The same pharmacology can impair new learning, working memory, divided attention, reaction time, and coordination; increase anxiety; or produce paranoid and psychotic-like experiences. Higher delivered dose generally increases the probability and magnitude of adverse acute effects, but the curve is modified by tolerance, route, and vulnerability (Broyd et al., 2016; Hindley et al., 2020).

In the liver, THC is oxidized largely through CYP2C9 and CYP3A4 pathways. 11-hydroxy-THC remains psychoactive and can cross the blood–brain barrier. Further oxidation yields 11-nor-9-carboxy-THC, commonly called THC-COOH, which is not intoxicating but is important in testing. Conjugated metabolites are eliminated in urine and feces. Because THC is lipophilic and redistributes into tissues, terminal elimination and detection are complex. A positive metabolite test is evidence of exposure, not a direct meter of current impairment.

CBD: different, not opposite

Cannabidiol is often described as “nonpsychoactive,” but *non-intoxicating* is more precise. At sufficient doses CBD can alter alertness, interact with medicines, affect liver enzymes, and change subjective or physiological states without producing the characteristic THC intoxication. It has low affinity for the orthosteric sites of CB1 and CB2. Proposed actions include negative allosteric modulation of CB1 in some systems, effects on endocannabinoid

tone, TRP channels, GPR55, PPAR-related signaling, adenosine transport, and serotonergic mechanisms. The relevance of each depends on concentration, tissue, and outcome; no single mechanism has earned the right to explain all CBD claims (Martinez Naya et al., 2024).

The strongest clinical evidence is not for low-dose wellness products. It is for a purified, standardized oral solution used at weight-based pharmaceutical doses for seizures associated with Dravet syndrome, Lennox–Gastaut syndrome, and tuberous sclerosis complex. Those trials also reveal why "CBD is harmless" is wrong: somnolence, diarrhea, appetite change, clinically important drug interactions, and hepatocellular enzyme elevations occur, particularly with some antiseizure medicines (Devinsky et al., 2017; Devinsky et al., 2018; Thiele et al., 2021; FDA, 2023).

CBD may modulate some THC effects under some conditions, but "CBD cancels THC" is not supported. Timing matters: pretreatment with a large oral dose is different from co-inhaling CBD and THC. Ratio matters because raising CBD while holding total plant material constant may simply reduce the THC dose. Recent randomized studies found no dependable, general protection from THC-related cognitive impairment, psychotic symptoms, or driving impairment; some measures were unchanged or worsened (Lawn et al., 2023; McCartney et al., 2022; Chesney et al., 2025). Earlier small studies reported protective signals. The honest conclusion is conditional and unsettled, not oppositional: CBD and THC are different molecules, and CBD is not an antidote.

Minor cannabinoids: the space between measurable and meaningful

Cannabigerol, CBG, is the neutral counterpart of CBGA and interacts with several targets in experimental systems. Cannabichromene, CBC, is non-intoxicating in the ordinary sense and has preclinical anti-inflammatory and analgesic signals. Tetrahydrocannabivarin, THCV, can show dose- and context-dependent interactions at cannabinoid receptors. Cannabidivarin, CBDV, has been studied for anticonvulsant and neurodevelopmental indications without an established general clinical role. CBN is a degradation-related cannabinoid with weak CB1 activity; marketing it as a proven sedative gets ahead of controlled evidence. Other cannabinoids—including acidic, propyl, and recently commercialized semi-synthetic compounds—expand the chemical catalog faster than human pharmacology can evaluate it (Stone et al., 2020; Walsh et al., 2021; Basavarajappa et al., 2024).

This is a recurring epistemic trap. Analytical chemistry can establish that a molecule exists. A receptor assay can establish activity at a concentration. An animal experiment can support a mechanistic possibility. None of those alone establishes a safe dose, a therapeutic indication, or a predictable effect in a retail mixture. "Bioactive" is not a synonym for "beneficial." It is a reason to investigate.

Terpenes and terpenoids

Terpenes contribute the volatile architecture of cannabis aroma: myrcene, limonene, α-pinene, β-caryophyllene, linalool, terpinolene, and many others can occur in varying proportions. Oxygenated or otherwise modified terpenes are often called terpenoids, although usage is inconsistent. β-caryophyllene has particular mechanistic interest because it can act at CB2 in experimental systems. Pinene, limonene, and linalool have pharmacology outside cannabis. Yet the fact that an isolated compound has an effect does not establish that its concentration in a product modifies THC intoxication in a clinically important way.

Volatiles also change with drying, storage, and heating. Combustion and high-temperature aerosolization create degradation products not present in the flower. A label based on a pre-use laboratory sample is therefore not a

complete description of inhaled chemistry. The chemistry that enters the lung is a transformation of the chemistry in the jar.

Flavonoids and the long tail

Cannabis contains flavonoids, pigments, fatty acids, sterols, waxes, and numerous other compounds. Cannflavins have attracted preclinical attention. Their presence is chemically interesting, but human exposure and pharmacology remain insufficiently characterized. The scientifically mature position is neither dismissal nor celebration. It is a structured unknown: identity may be established; concentration may be measured; target activity may be plausible; clinically meaningful effect remains unproven.

The entourage effect: interaction is not automatically synergy

The “entourage effect” can mean at least four different things. It can mean that two constituents interact pharmacokinetically. It can mean that one changes another's receptor effect. It can mean that a mixture has a larger benefit or smaller harm than a matched dose of its major component. Or it can function as a commercial story that a whole-plant product is inherently wiser than an isolated molecule. These are different hypotheses.

Interactions certainly exist. THC and CBD can alter one another's metabolism under some conditions. Minor constituents can bind relevant targets. Aroma changes expectation, and expectation changes experience. But robust synergy requires an appropriate comparator: matched THC dose, matched route, blinding, validated outcomes, and enough participants to estimate an interaction. Much of the literature lacks those features. Critical reviews conclude that particular combinations deserve study while a general, predictable clinical entourage effect remains unestablished (Ferber et al., 2020; Christensen et al., 2023; André et al., 2024).

The claim can be expressed formally. If the effect of a mixture containing A and B is **E(A,B)**, synergy is not demonstrated merely because **E(A,B) > E(A)**. The B-containing preparation may deliver a different dose or change absorption. A defensible interaction test asks whether:

$$E(A,B) - E(0,0) > [E(A,0) - E(0,0)] + [E(0,B) - E(0,0)]$$

on a prespecified effect scale, or uses another justified interaction model. The scale matters. A combination can appear synergistic on an additive scale and not on a multiplicative one. The equation is useful because it exposes what marketing language usually omits: a counterfactual.

3. Potency, dose, and the remaking of the product Back to TOC

A market-level experiment

Cannabis has changed through deliberate selection, improved cultivation, extraction, and commercialization. In the US federal Potency Monitoring Program, average THC in seized plant samples increased from 3.96 percent in 1995 to 16.14 percent in 2022, while average CBD in the 2022 samples was 0.12 percent. The sample count also fell from 3,763 to 351, and law-enforcement seizures are not a probability sample of everything people used. The trend is nevertheless large and consistent with other surveillance: contemporary users can access flower with high-teens or twenty-plus-percent THC and concentrates commonly above 60 percent (NIDA, 2024; Lake et al., 2025).

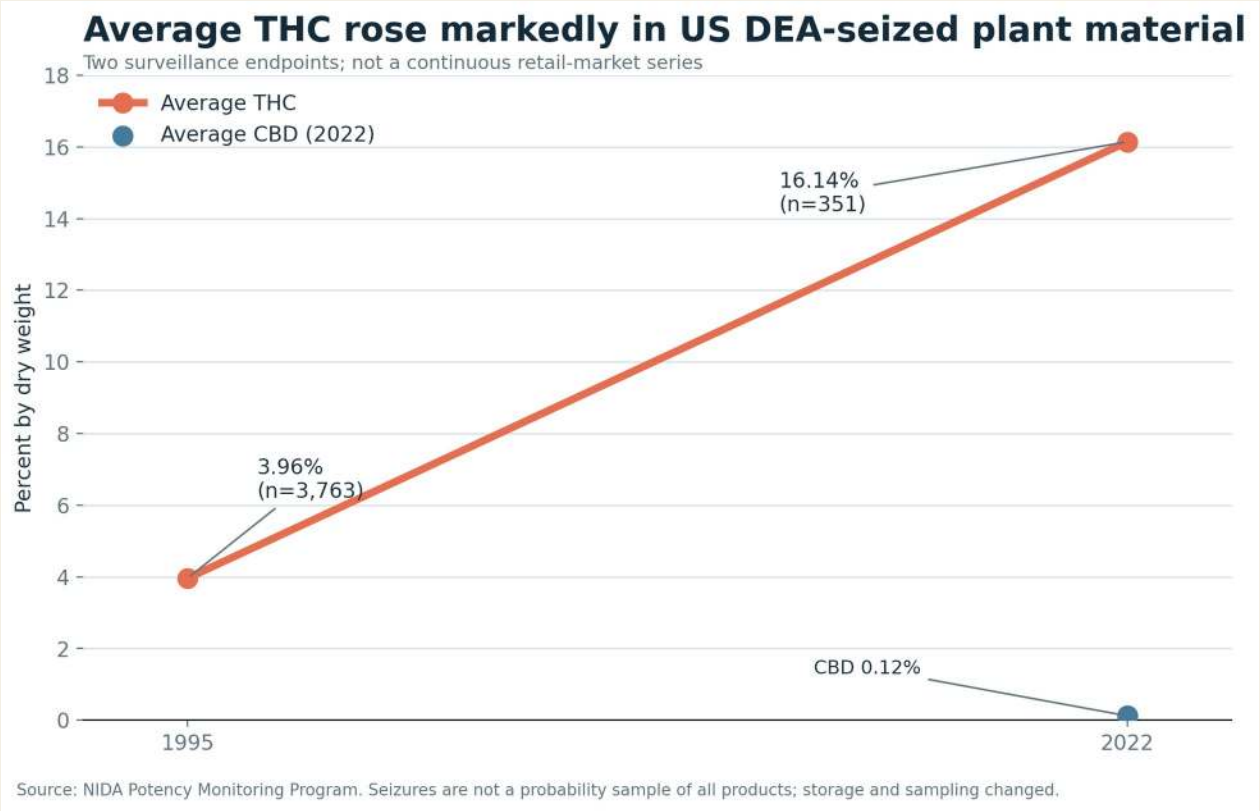

Figure 3. Average THC and CBD in US DEA-seized plant material, 1995–2022. The figure shows surveillance averages, not the potency of every retail or illicit product. Source: NIDA Potency Monitoring Program.

Historical comparison requires care. Older samples can lose THC in storage. Cultivation and sampling differ by era. Users may titrate by taking less of a stronger product. A joint is not a standardized unit, and concentrate mass is not comparable with flower mass. But titration is incomplete, especially with rapid boluses or delayed edibles. Higher concentration increases the possible delivered dose and reduces the margin for error.

Potency is not dose—but it shapes dose

Concentration answers “how much THC per unit mass or volume?” Dose answers “how much THC was administered?” Absorbed dose asks how much crossed into systemic circulation. Brain exposure adds distribution over time. Functional dose is the resulting perturbation of cognition or behavior in this individual. These can diverge.

If a product contains a mass fraction *p* of THC and an amount *m* is used, the nominal THC content is:

$$D_n = p \times m.$$

Absorbed dose can be represented as $D_a = F \times D_n$, where *F* is bioavailability. But *F* is not a constant of the person: it changes with route, device, inhalation pattern, formulation, food, and first-pass metabolism. A neat calculation from a label can therefore carry false precision.

The relationship between dose and effect is often approximated with a Hill function:

$$E(D) = E_0 + Emax \cdot D^h / (EC_{50}^h + D^h).$$

This makes two important points. Response can rise steeply around a threshold rather than linearly. And two people can have different EC_{50}, Emax, or slope *h*. The equation is a teaching model, not a validated personal dosing tool.

Why high potency matters clinically

High potency can increase acute anxiety, disorganization, memory impairment, and psychotic-like effects by enabling larger or faster THC exposure. Repeated high-potency use is associated most consistently with Cannabis Use Disorder and psychosis-related outcomes. In the multicentre EU-GEI study, daily use of high-potency cannabis was associated with markedly greater odds of first-episode psychotic disorder than never use; later systematic reviews find the clearest high-potency harm signal for psychosis and CUD, with less consistent evidence for depression or anxiety (Di Forti et al., 2019; Petrilli et al., 2022; Lake et al., 2025; Rittiphairoj et al., 2025).

Association is not an assay of causality. People who choose stronger products may differ in prior tolerance, symptoms, risk-taking, social context, and cumulative use. Potency is often inferred from a local market category rather than measured in the product used. Yet the convergence of acute dose-response, receptor pharmacology, frequency gradients, and high-potency observational data makes it unreasonable to treat concentration as irrelevant.

Concentrates also change behavior. A compact product can be used discreetly and repeatedly. Rapid delivery can strengthen the temporal link between action and reward. Tolerance can make a dose feel ordinary while impairment remains relevant in complex tasks. Withdrawal can become more apparent when repeated exposure stops. These are plausible pathways, but product-specific longitudinal research still lags behind the market.

Ratio is information, not immunity

THC:CBD ratio can be useful, especially when accompanied by absolute concentrations. A 1:1 product containing 2.5 milligrams of each compound is not equivalent to one containing 50 milligrams of each. A high ratio may signal little CBD relative to THC, but it does not say how much THC was taken. A low ratio can result from high CBD, low THC, or both.

CBD content may be a marker of lower THC in some botanical products and could modulate selected effects in selected conditions. It does not neutralize high THC. The safest inference from a product with less THC is usually that it exposes the user to less THC—not that another constituent creates a pharmacological shield.

Product uncertainty is part of exposure

Inaccurate cannabinoid labels and contaminants create a second layer of uncertainty. Pesticides can concentrate during extraction. Cannabis can accumulate metals from soil or equipment. Microbial contamination matters especially for immunocompromised people. Residual solvents reflect manufacturing rather than cannabinoid pharmacology. Unregulated products may contain undeclared THC, semi-synthetic cannabinoids, or synthetic cannabinoid receptor agonists. Each failure requires its own causal language (Dryburgh et al., 2018; Jameson et al., 2022; Gidal et al., 2024).

It is therefore useful to separate three risk columns. **Intrinsic cannabinoid risk** includes THC intoxication, impairment, dependence, and psychiatric effects. **Route risk** includes combustion products and inhalation injury.

Production and regulatory risk includes contamination, mislabeling, appealing packaging, inconsistent serving sizes, and unknown mixtures. A policy can reduce one column while increasing or leaving another unchanged.

The first synthesis

The plant chapter ends with an apparently modest conclusion that will govern the rest of the book: “cannabis use” is not a sufficiently specified scientific exposure. The minimum informative unit is a product–dose–route–time event embedded in a person and a setting. When frequency and history are added, that event becomes a trajectory. Neuroscience begins not with a culture-war category but with this trajectory meeting the endocannabinoid system.

Part II — The regulatory system cannabis enters Back to TOC

4. The endocannabinoid system: control by local demand Back to TOC

Not a “cannabis system”

The endocannabinoid system did not evolve so that a plant could intoxicate humans. It is an ancient signaling architecture distributed through the nervous system, immune system, gut, reproductive tissues, adipose tissue, bone, liver, and other organs. Its components participate in appetite, pain, stress recovery, movement, memory, synaptic plasticity, immune regulation, and energy balance. The word *system* is useful, but it can mislead if it suggests one centrally commanded pathway. Endocannabinoid signaling is often local, short-lived, cell-specific, and dependent on what a circuit has just been doing.

Three elements form its classical core. Cannabinoid receptors—especially CB1 and CB2—receive signals. Endogenous ligands—notably anandamide and 2-arachidonoylglycerol, or 2-AG—carry them. Enzymes synthesize and remove those ligands. Around that core sits a wider network of lipid mediators, ion channels, nuclear receptors, transport processes, and metabolic enzymes. Boundaries therefore depend on the question being asked (Di Marzo and Piscitelli, 2015; Lu and Mackie, 2016; Zou and Kumar, 2018).

CB1 is among the most abundant G-protein-coupled receptors in the mammalian brain. It is commonly located on presynaptic terminals, where activation reduces the probability of neurotransmitter release through Gi/o-linked signaling, inhibition of adenylyl cyclase, modulation of calcium and potassium channels, and downstream kinase pathways. CB2 is prominent in immune cells and is also expressed in the nervous system, especially in immune-like and glial populations and under some pathological conditions. The old slogan “CB1 in brain, CB2 in body” is therefore an introductory approximation, not a map.

Retrograde signaling: the receiving neuron speaks backward

Conventional textbook transmission runs from a presynaptic neuron to a postsynaptic neuron. Many endocannabinoid events run in the other direction. Strong postsynaptic activity, membrane depolarization, or activation of particular Gq/11-coupled receptors can increase intracellular calcium or stimulate lipid-signaling enzymes. The postsynaptic cell then synthesizes an endocannabinoid on demand. The lipid crosses the narrow synaptic space, engages CB1 on the presynaptic terminal, and temporarily lowers transmitter release.

This is retrograde synaptic control: the receiving neuron tells the sending terminal, in effect, to reduce its output. It can suppress GABA release—depolarization-induced suppression of inhibition—or glutamate release—depolarization-induced suppression of excitation. The sign of the network effect depends on which terminal is regulated. Suppressing an inhibitory GABA terminal can disinhibit the next neuron and raise its firing. Suppressing an excitatory glutamate terminal can lower its drive. “CB1 inhibits neurotransmission” is molecularly reasonable and circuit-level incomplete.

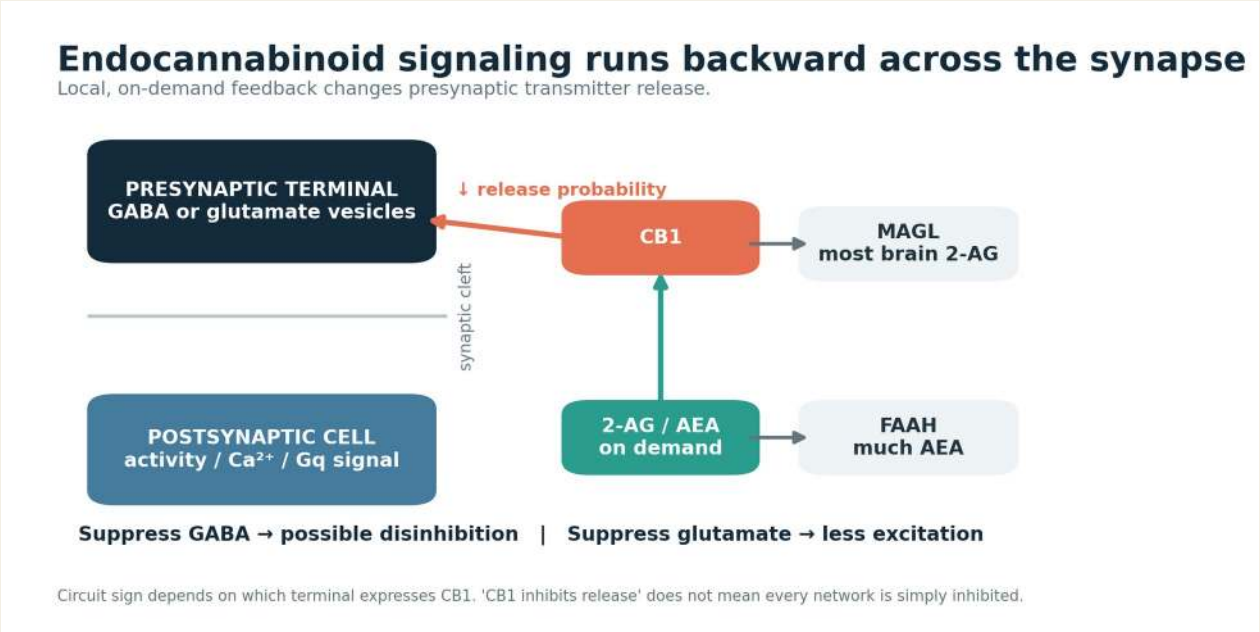

Figure 4. The endocannabinoid synapse. Postsynaptic activity drives on-demand lipid synthesis. 2-AG or anandamide travels retrogradely to presynaptic CB1, reducing transmitter release. MAGL removes much of presynaptic 2-AG; FAAH removes much anandamide, chiefly postsynaptically. Whether the circuit is functionally excited or inhibited depends on the identity of the regulated terminal.

This architecture is suited to gain control and homeostasis. It can constrain excessive excitation, reshape the timing of inhibition, select active synapses, and participate in short- and long-term plasticity. Yet “homeostatic” does not mean that any external cannabinoid restores balance. A thermostat's existence does not make every hand placed on it corrective. Endocannabinoids are generated in particular cellular compartments for limited periods. Inhaled or ingested THC reaches many receptors across many regions on a different time course.

Anandamide and 2-AG are not interchangeable

Anandamide, formally *N*-arachidonoylethanolamine and often abbreviated AEA, is a partial agonist at CB1 with activity at other targets including TRPV1 under some conditions. It is commonly synthesized from membrane-associated precursors through several possible routes and is hydrolyzed largely by fatty-acid amide hydrolase, FAAH. AEA often behaves as a lower-abundance, event-specific signal, although that phrase cannot capture its tissue diversity.

2-AG is generally more abundant in brain tissue and functions as a full agonist at CB1 and CB2 in many assays. Postsynaptic diacylglycerol lipase, especially DAGLα, is a major synthetic route. Monoacylglycerol lipase, MAGL, accounts for much 2-AG hydrolysis, with ABHD6 and ABHD12 contributing. MAGL is enriched in presynaptic terminals and astrocytes; FAAH is commonly postsynaptic. This spatial complementarity helps terminate signals near where they act.

The shorthand is useful only if its limits remain visible. AEA and 2-AG concentrations vary by region and physiological state. The same enzymes participate in broader lipid metabolism. Blocking FAAH or MAGL changes more than one molecular number. In 2016, a catastrophic phase I trial of the FAAH inhibitor BIA 10-2474 caused severe neurological injury and one death; the toxicity is not thought to establish that selective FAAH inhibition as a class is inherently dangerous, but it is a durable warning against translating a clean pathway cartoon into assumptions about a drug (Kerbrat et al., 2016).

A system that changes with experience

Endocannabinoid signaling is plastic. Stress, feeding, exercise, circadian timing, pain, inflammation, reproductive hormones, and drug exposure can alter ligand levels, receptor availability, or enzyme expression. Repeated THC exposure can reduce CB1 receptor availability and signaling efficiency. Human positron-emission tomography has found lower cortical CB1 availability in chronic daily users, with substantial normalization over weeks of monitored abstinence in small studies (Hirvonen et al., 2012).

That recovery is scientifically important. It is evidence of adaptation, not proof of permanent receptor loss. It also helps explain tolerance and withdrawal. When exogenous agonist exposure is repeated, the system adjusts. When exposure stops abruptly, the adapted system no longer receives the expected input. Irritability, sleep disruption, vivid dreams, appetite change, anxiety, dysphoria, restlessness, and craving can emerge while regulation recalibrates. Molecular adaptation is one layer of dependence; learned routines, cues, relief, relationships, and identity are others.

5. A circuit map: where local modulation becomes experience Back to TOC

Distribution is not destiny

CB1 density is high in cortex, hippocampus, basal ganglia, and cerebellum, and important in amygdala, hypothalamus, brainstem nuclei, spinal cord, peripheral nerves, and autonomic circuits. Receptor density is not a simple heat map of subjective effect. Cell type and synaptic position matter. CB1 can be especially abundant on cholecystokinin-positive GABA interneurons in cortex and hippocampus, while also regulating glutamatergic terminals. A low-density strategic site can matter greatly; a high-density region can contribute differently depending on the task.

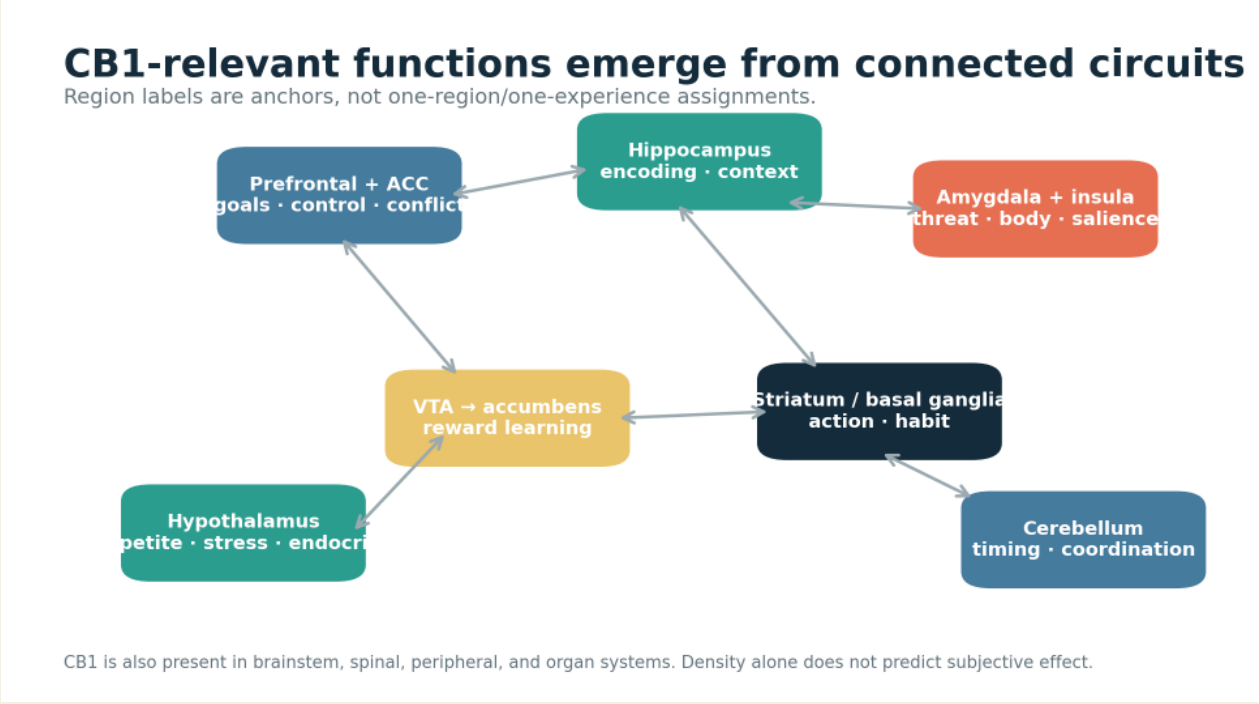

Figure 5. CB1-relevant circuitry and functions. The map links regions to experimentally supported functions without assigning one region to one experience. Prefrontal, hippocampal, amygdalar, striatal, mesolimbic, hypothalamic, cerebellar, insular, and cingulate effects emerge through connected networks.

The prefrontal cortex coordinates working memory, rule maintenance, inhibition, planning, valuation, and context-sensitive behavior. THC does not simply "turn off" a prefrontal module. By altering excitation–inhibition balance, oscillatory coordination, and input from hippocampal, thalamic, striatal, and dopaminergic systems, it can reduce the stability of task representations. A thought can feel salient and novel while the ability to hold its premises together deteriorates.

The hippocampal formation helps encode relations among places, events, and context. Dense CB1 expression and endocannabinoid involvement in plasticity make it especially relevant to THC-related impairment of episodic and verbal learning. Acute THC reliably interferes with the encoding of new information; retrieval of well-learned information may be less affected. The familiar experience—an insight appears, attention moves, and the beginning of the thought is lost—can be understood as a failure to maintain and bind information, not as literal destruction of memory cells.

The amygdala participates in threat learning, salience, and emotional interpretation. The anterior cingulate and insula integrate uncertainty, bodily state, error, pain, conflict, and salience. THC-related anxiety or paranoia likely does not originate in one "fear center." It can arise when ambiguous internal or social signals acquire heightened significance while contextual control and memory become less reliable. In a safe setting, altered salience may feel comic or profound. In a vulnerable or sleep-deprived state, it may feel like evidence that others are watching.

The cerebellum and basal ganglia help coordinate timing, movement, action selection, and learned sequences. CB1 modulation in these circuits contributes to slowed reaction, altered timing, tracking errors, and impaired coordination. Subjective confidence may not fall in proportion to performance. This mismatch is one reason driving cannot be reduced to whether a person feels "high."

The hypothalamus integrates energy state, stress, endocrine signals, temperature, and motivated behavior. Endocannabinoid signaling can promote feeding and alter neuroendocrine responses. Acute appetite stimulation is real; broad claims that ordinary cannabis exposure permanently deranges specific hormones are much less secure. Effects depend on dose, chronicity, sex, reproductive state, sampling time, and confounding.

Mesolimbic dopamine: an indirect route to reward

The ventral tegmental area, or VTA, sends dopamine projections to the nucleus accumbens, prefrontal cortex, amygdala, and other targets. THC does not act like a dopamine transporter blocker. It can increase mesolimbic dopamine indirectly, in part by activating CB1 receptors on inhibitory terminals and disinhibiting dopamine neurons, while glutamatergic inputs and local microcircuits also change. Human imaging shows smaller and more variable dopamine release than classic stimulants. In people with chronic heavy use or CUD, some studies find blunted striatal dopamine synthesis or release, but results are heterogeneous (Ahrens et al., 2025).

This nuance matters for addiction. A drug need not generate an enormous dopamine spike to become reinforcing. Rapid relief, cue association, social reward, sensory enhancement, and avoidance of withdrawal can teach repetition. Dopamine is involved in learning about motivational significance and prediction error, not a meter labeled "pleasure." Repeated cannabis use can become highly valued even when the acute experience has become less euphoric.

CB2, glia, immunity, and the danger of extrapolation

CB2 receptors and cannabinoid-sensitive immune pathways have legitimate relevance to inflammation, pain, and neuroimmune signaling. Microglia and astrocytes respond to injury and participate in synapse maintenance.

Preclinical studies suggest that cannabinoid manipulations can alter cytokines, microglial phenotype, oxidative stress, and neuroinflammation. Effects vary with ligand, cell state, dose, and disease model; some are protective, others harmful or biphasic.

It would be a category error to move from “a CB2 agonist reduced inflammation in a rodent model” to “cannabis protects the human brain.” THC, CBD, endogenous ligands, and selective experimental compounds are not interchangeable. A disease model is not the disease. Immune signaling is a frontier discussed later, not a settled explanation for the cognitive or psychiatric outcomes of human cannabis use.

Beyond CB1 and CB2

CBD and several endogenous lipids interact with targets outside classical cannabinoid receptors. TRPV1 is a nonselective cation channel involved in heat, nociception, and plasticity; anandamide can activate it, and CBD can modulate multiple TRP channels in experimental systems. GPR55 is sometimes called an orphan or putative cannabinoid receptor, but its endogenous role and the clinical relevance of cannabinoid actions there remain unsettled. PPARα and PPARγ are nuclear receptors involved in metabolism and inflammation. CBD may influence adenosine signaling partly by limiting cellular uptake, and 5-HT1A-linked mechanisms have been proposed for anxiety-related effects.

These mechanisms are plausible, concentration-dependent, and incompletely mapped in humans. A molecule acting on many targets is not automatically a “multifunctional medicine.” Polypharmacology can support benefit, adverse effects, interactions, or no clinically meaningful effect at the achieved concentration. Throughout this book, target evidence is not allowed to substitute for an outcome trial.

6. THC and CBD: a comparison without caricature Back to TOC

Two molecules, different questions

THC and CBD are often placed at opposite ends of a single axis: intoxicating versus calming, dangerous versus safe, recreational versus medical. That picture is attractive and wrong. THC is a partial agonist at CB1 and CB2 whose central CB1 actions are chiefly responsible for cannabis intoxication. CBD has low orthosteric affinity for those receptors and a broader, less settled pharmacology. They can coexist in a plant and interact pharmacokinetically or pharmacodynamically, but one is not the molecular negation of the other.

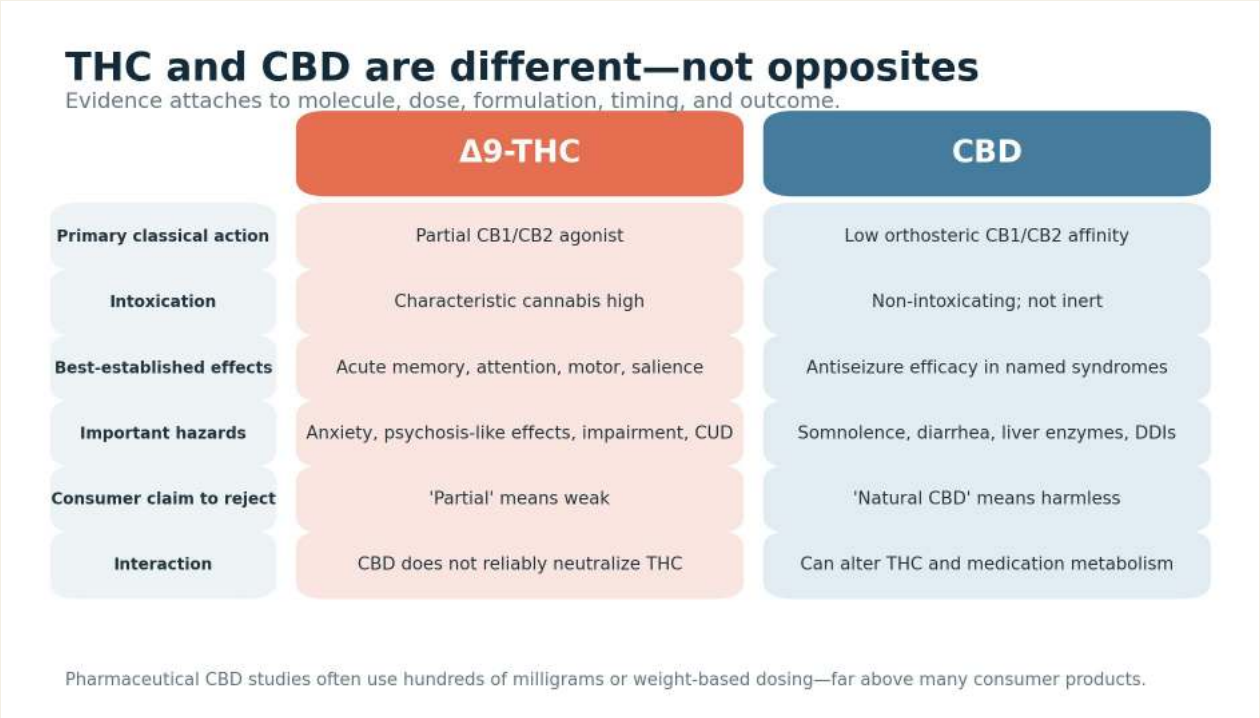

Figure 6. THC and CBD compared. The panel separates receptor pharmacology, intoxication, established indications, acute hazards, dose ranges studied, interaction uncertainty, and monitoring requirements. “Non-intoxicating” is not “inert,” and “partial agonist” is not “weak.”

Acute THC effects are dose-responsive at the group level. In controlled experiments, THC can increase self-rated intoxication, anxiety, suspiciousness, perceptual alteration, and psychosis-like symptoms while impairing verbal learning, working memory, divided attention, and motor coordination. Average effects conceal wide distributions. A modest dose can be pleasant to one participant and dysphoric to another. Prior exposure shifts the curve through tolerance, but does not reliably restore complex performance to baseline.

THC can alter salience: ordinary sensations or ideas may feel unusually meaningful. It can change time estimation, making short intervals feel extended. It can narrow the field of attention while increasing absorption in selected stimuli. These effects help explain both attraction and hazard. Music may feel layered; a trivial bodily sensation may become alarming. An association may feel revelatory while its logical quality deteriorates. Science should not deny the pleasure in order to describe the impairment.

Memory, attention, and the problem of encoding

The most reproducible cognitive effects of acute THC concern learning and memory, especially encoding. Working memory requires information to remain accessible while it is manipulated. Episodic learning requires attention to bind items with context. THC-related disruption in hippocampal–prefrontal coordination can impair both. This does not mean every intoxicated person is globally amnesic. It means the probability of omission, intrusion, distraction, and poor acquisition rises.

Attention is not one faculty. Sustained attention, selective attention, divided attention, and attentional control can dissociate. A user may sustain intense focus on one stimulus while failing to notice a pedestrian, conversational cue, or changing task rule. In laboratory studies, performance costs depend on dose, task difficulty, tolerance, and time since exposure. Easy tasks can miss impairment that appears when demands rise.

Anxiety, paranoia, and psychotomimetic effects

THC can be anxiolytic or relaxing at lower exposure in some people and anxiogenic at higher exposure, a pattern often described as biphasic. A neat U-shaped curve should not be treated as an individual calculator. Baseline anxiety, expectation, social threat, dose, route, and prior adverse experiences all move the curve. Panic can be amplified by tachycardia: a normal acute drug effect is interpreted as danger, attention locks onto the body, and fear escalates.

Paranoia is not synonymous with psychosis. It can range from transient social suspiciousness with retained insight to a fixed persecutory belief. Controlled THC administration can transiently increase positive psychotic symptoms in healthy volunteers, providing experimental evidence that THC can produce psychotomimetic states (Hindley et al., 2020). Cannabis-induced psychotic disorder is a clinical syndrome in which delusions or hallucinations are prominent and exceed ordinary intoxication. Schizophrenia-spectrum illness is a broader and often persistent disorder. Collapsing the three exaggerates some claims and obscures others.

Reward, appetite, pain, and movement

THC can enhance the incentive value of food and sensory experience and can reduce some forms of pain. Analgesia is not uniform: nociceptive intensity, unpleasantness, inflammation, neuropathic mechanisms, expectation, and sedation may change differently. In clinical trials, cannabinoid benefits for chronic pain are usually small on average and accompanied by dizziness, sedation, nausea, and cognitive adverse effects. A statistically detectable mean improvement is not necessarily a large personal benefit.

CB1 signaling in cerebellar and basal-ganglia circuits contributes to impaired timing and coordination. At very high exposure, especially in inexperienced users or children, profound somnolence, vomiting, ataxia, confusion, or agitation can occur. Fatal isolated THC poisoning appears rare, but “rarely fatal by itself” is a poor synonym for safe. Injury, aspiration, cardiac stress, psychosis, and combined-substance effects do not require a classic lethal receptor mechanism.

Tolerance, dependence, and withdrawal

Tolerance is a reduced effect after repeated exposure or a need for more exposure to obtain a prior effect. It develops at different rates for different outcomes. A daily user may report little subjective intoxication while still showing impairment on demanding tasks. Cross-sectional comparisons can therefore confuse tolerance with absence of effect.

Physical dependence means that stopping an adapted exposure produces withdrawal. It is neither identical to addiction nor proof of moral failure. Cannabis withdrawal is well characterized: irritability or anger, sleep difficulty and vivid dreams, anxiety, decreased appetite or weight, restlessness, depressed mood, and physical discomfort can occur. Symptoms often begin within one or two days, peak during the first week, and improve over one to two weeks, although sleep disturbance and craving may last longer in heavy users. Cannabis Use Disorder adds impaired control, craving, priority given to use, persistence despite harm, and functional consequences. Chapter 14 treats it in depth.

CBD at clinical and consumer scales

The contrast between pharmaceutical and consumer CBD is a contrast in dose, purity, formulation, indication, and monitoring. In pivotal epilepsy trials, purified CBD was commonly studied around 10–20 mg/kg/day; a 70-

kilogram adult equivalent would be hundreds to more than a thousand milligrams per day, although epilepsy dosing is not transferred by simple arithmetic to another condition. Consumer drinks, gummies, or oils may contain single- or double-digit milligram amounts, sometimes inaccurately labeled. Evidence obtained with a standardized prescription solution cannot be attached to a low-dose retail product by using the same three letters.

CBD's antiseizure efficacy in Lennox–Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex is well established for the approved formulation and populations. Mechanism is not fully reduced to one target. Efficacy can partly interact with other antiseizure drugs—most notably clobazam—but benefits are not only a metabolite artifact. Somnolence is more common with clobazam. Transaminase elevations are more common with valproate, and the product label requires liver monitoring under specified circumstances (FDA, 2023).

Evidence for anxiety is much thinner. Small experiments, including simulated public speaking, have produced signals, often at hundreds of milligrams and sometimes with an inverted-U pattern. Trials vary in diagnosis, acute versus chronic dosing, outcome, and risk of bias. A 2026 systematic review of randomized trials did not establish cannabinoids as effective treatments for anxiety disorders, PTSD, psychotic disorders, or opioid use disorder (Wilson et al., 2026). “Promising” should not be promoted to “proven.”

Antipsychotic signals are similarly preliminary. One adjunctive trial of 1,000 mg/day CBD found a modest improvement in clinician-rated positive symptoms; other trials and syntheses have been inconsistent (McGuire et al., 2018). These data do not justify replacing antipsychotic treatment with consumer CBD. They do show that a non-intoxicating cannabinoid can be studied as a molecule rather than as a cultural category.

Does CBD protect against THC?

The interaction depends on sequence and dose. CBD can inhibit enzymes that metabolize THC and may, in some circumstances, increase or prolong THC exposure. It may also modify CB1 signaling or anxiety-related processes. In balanced products, a lower THC dose may account for some apparent tolerability. Human experiments have reported protection, no protection, and occasional enhancement of adverse effects. Larger, better controlled recent studies make a universal protective rule untenable (Lawn et al., 2023; McCartney et al., 2022; Chesney et al., 2025).

A scientifically adequate comparison holds THC constant while varying CBD, measures blood concentrations, preserves blinding, and samples more than one time point. Many naturalistic comparisons do none of these. The practical conclusion is narrow: CBD should not be relied upon to make a high THC exposure safe, to restore driving ability, or to prevent psychosis.

7. Pharmacokinetics: the route writes the clock Back to TOC

From administered amount to effect

Pharmacokinetics asks what the body does to a compound: absorption, distribution, metabolism, and elimination. Pharmacodynamics asks what the compound does to the organism. The two are linked but not interchangeable. Blood concentration is a partial proxy for effect-site exposure. Brain concentration cannot be measured routinely. Subjective intoxication, cognitive impairment, heart rate, and anxiety can peak at different times. Tolerance and task demands can uncouple them further.

For an idealized one-compartment model after absorption, concentration declines as

$$C(t) = C_0 e^{(-kt)}, \quad t_{1/2} = \ln(2)/k.$$

THC does not behave as a perfect one-compartment drug. Rapid distribution into highly perfused tissues is followed by redistribution into fat and slower terminal release. The equation clarifies exponential decay; it does not justify estimating impairment from a single half-life. An effect-compartment model can represent delay between plasma and effect:

$$dC_e/dt = k_{e0}[C_p(t) - C_e(t)],$$

where C_p is plasma concentration and C^e is an unobserved effect-site concentration. Even that model cannot encode expectation, tolerance, or task complexity.

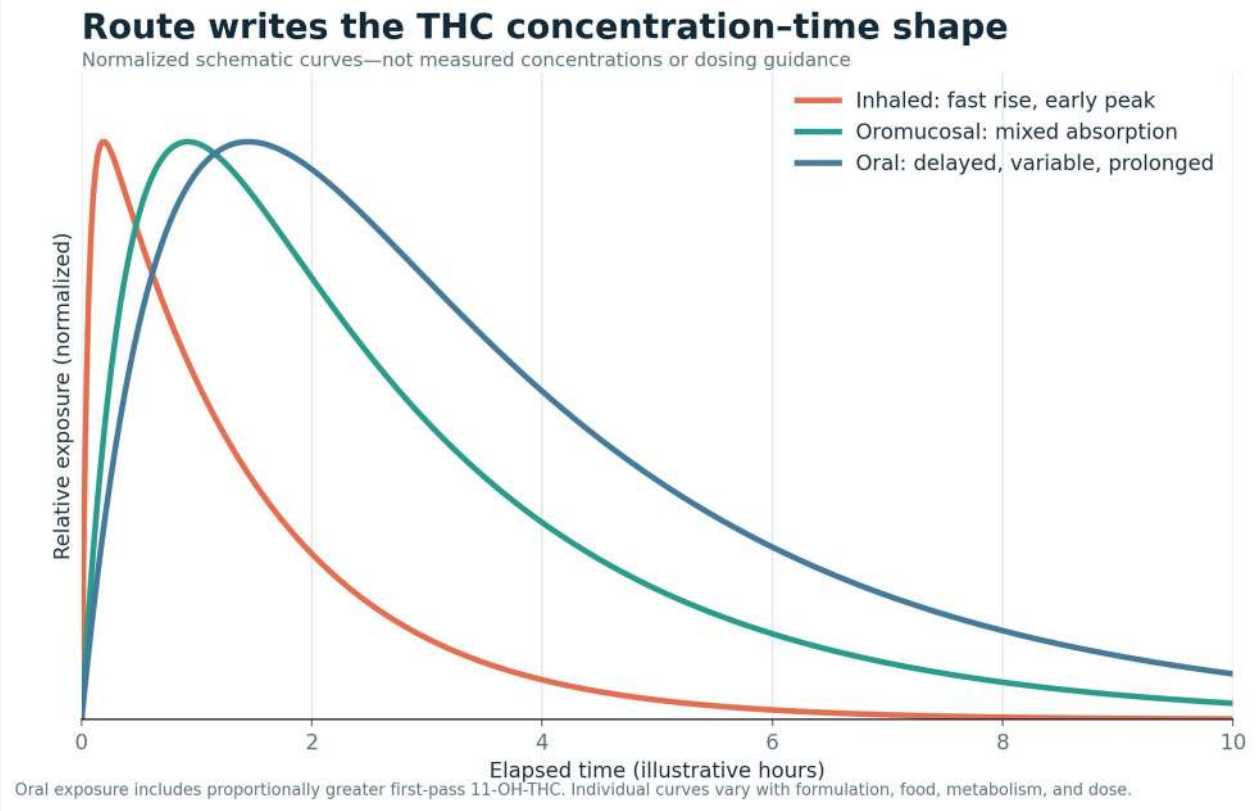

Figure 7. Schematic route-dependent THC time courses. Inhalation produces a rapid, high early peak and faster subjective onset; oral administration is slower, more variable, and longer, with greater first-pass formation of 11-OH-THC. Curves are normalized teaching schematics, not personal dosing predictions.

Smoking

Combustion releases cannabinoids into smoke and creates carbon monoxide, fine particulates, irritants, and carcinogenic compounds. Pulmonary absorption is rapid. THC reaches blood within minutes, subjective effects begin quickly, and users can partly adjust subsequent inhalation based on early feedback. Bioavailability is variable—often summarized around 10–35 percent—because puff volume, breath holding, sidestream loss, device, combustion temperature, and experience differ (Huestis, 2007; Lucas et al., 2018).

Peak venous THC can occur before or near the end of smoking and then falls rapidly as THC distributes into tissues, even while intoxication continues. This counterclockwise hysteresis is one reason a blood value has

different meanings depending on whether it was obtained on the rising or falling limb. Chronic users can retain measurable THC after subjective effects have waned.

Vaporization and concentrates

Vaporization heats material or extract without intended combustion. It can reduce exposure to some combustion products but does not remove THC-related impairment, airway irritation, device contaminants, thermal degradation products, or the possibility of a large rapid dose. Delivery efficiency varies by device and temperature. Concentrate devices can deliver high THC mass in a few inhalations. “Vaping” also covers chemically different systems: dry-herb vapor, regulated oil cartridges, and illicit cartridges with diluents or contaminants should not be treated as one exposure.

The 2019 outbreak of e-cigarette or vaping-associated lung injury was strongly linked to vitamin E acetate in illicit THC products in the United States. That event illustrates a manufacturing hazard rather than an intrinsic effect of THC, while also showing why product source cannot be separated from route risk. Dabbing—a rapid inhalation of heated concentrate—combines high concentration, fast delivery, and variable technique. It is relevant to risk assessment; this book does not provide instructions for performing it.

Oral products and 11-hydroxy-THC

Swallowed THC has low and variable bioavailability, often estimated around 4–20 percent, because absorption is inconsistent and the liver metabolizes part of the dose before systemic circulation. Food and formulation can change exposure. Onset is commonly tens of minutes to more than two hours, peak effects may occur several hours after ingestion, and impairment can persist much longer than after inhalation. Interindividual variability is large (Lucas et al., 2018; Poyatos et al., 2020).

First-pass metabolism produces proportionally more 11-OH-THC than inhalation. This metabolite is psychoactive and crosses the blood–brain barrier. The oral experience is therefore not merely a delayed version of smoking. A slow rise can conceal the accumulating dose, a later peak can feel unexpectedly intense, and a long tail can outlast planned activities. Edibles are prominent in accidental pediatric exposures because a child may recognize candy rather than a drug, and a single package may contain multiple adult servings.

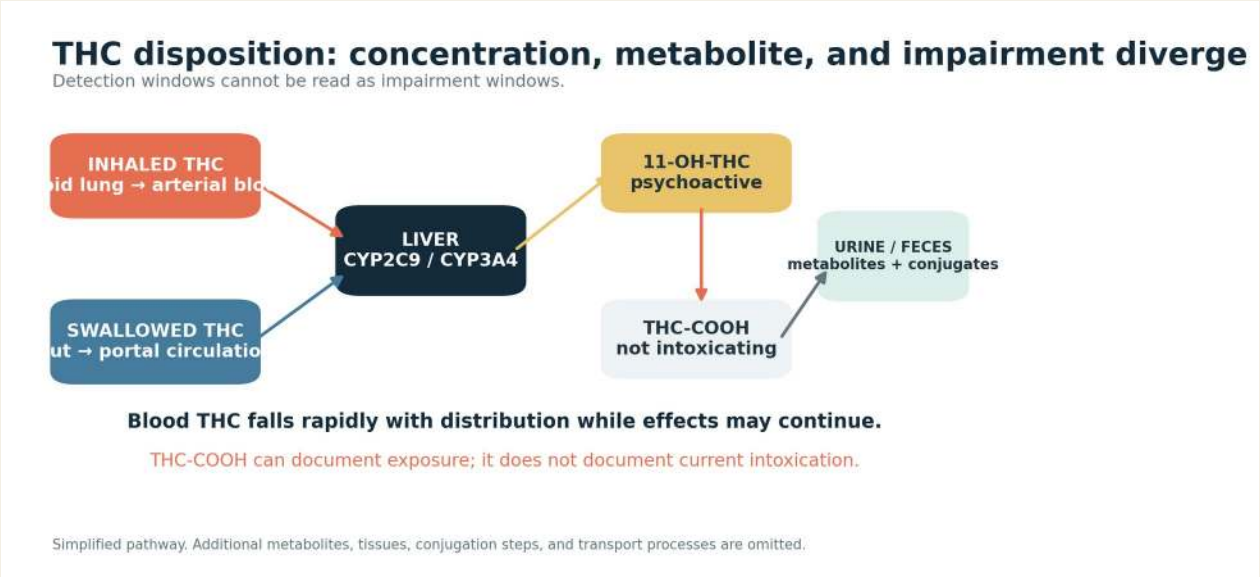

Figure 8. THC disposition. Inhaled THC rapidly reaches arterial blood and brain; swallowed THC first passes through gut and liver. CYP2C9 and CYP3A4 contribute to formation of active 11-OH-THC, followed by largely non-intoxicating THC-COOH and conjugates. Detection windows are not impairment windows.

Oromucosal, “sublingual,” and oils

Standardized oromucosal sprays aim to provide some absorption through oral mucosa while part of the dose is swallowed. Consumer tinctures placed under the tongue can likewise combine routes. Formulation, droplet placement, contact time, saliva, and swallowing produce variability. Onset is usually less immediate than inhalation and may not be much faster than oral use in real-world conditions. A product being called “sublingual” does not establish its bioavailability.

Oils alter solubility and gastrointestinal absorption. Nanodispersions and emulsions may increase exposure, which can make products more consistent but also makes milligram equivalence across formulations unreliable. CBD is especially sensitive to food effects; a high-fat meal can substantially increase exposure to pharmaceutical CBD. The relevant unit is not just milligrams printed on a label but milligrams in a specific formulation taken under specified conditions.

Topical and transdermal preparations

Topical preparations are intended to act near skin or superficial tissue. Evidence for analgesic efficacy is limited and products vary widely. Ordinary topical CBD or THC should not be assumed to produce substantial systemic exposure. A true transdermal system uses formulation technology to move drug across skin into circulation; that is a different claim requiring pharmacokinetic demonstration. Labels often blur the distinction.

Distribution, metabolism, and testing

THC is highly lipophilic, extensively protein bound, and distributed rapidly. It is metabolized through hepatic enzymes and eliminated mostly as metabolites in feces and urine. CBD is also lipophilic and extensively metabolized, involving CYP2C19, CYP3A4, and other pathways. Both can participate in drug interactions; CBD is the more prominent inhibitor at pharmaceutical exposure.

Blood THC declines much faster than the body's total burden. Urine immunoassays commonly detect THC-COOH and cannot determine when intoxication occurred. Hair testing has long windows and contamination concerns. Oral-fluid testing better reflects recent exposure but still does not directly measure impairment. No biological threshold has the simple interpretability of blood alcohol concentration. Per-se THC driving limits therefore trade administrative clarity for biological imprecision (Behzad et al., 2025).

Four quantities that must not be collapsed

Administered dose is the nominal amount taken. **Systemic exposure** is often summarized by concentration–time area under the curve. **Brain exposure** is the time-varying amount at relevant neural sites. **Functional impairment** is an outcome observed in a task or behavior. Product labels estimate the first, blood samples imperfectly index the second, neither directly gives the third, and none guarantees the fourth. A person can have a low measured blood value after a delay yet remain impaired; a frequent user can have a measurable value with little subjective intoxication.

This separation resolves an apparent contradiction. Blood concentration matters—without exposure there is no drug effect—but a single concentration has weak individual-level specificity because timing, route, distribution, tolerance, and measurement all matter. The right conclusion is not that toxicology is useless. It is that toxicology must be interpreted with history, examination, behavior, and time.

The route is a learning variable

Route changes more than chemistry. A rapidly delivered effect more tightly couples a behavior with its consequence, which can strengthen reinforcement learning. A delayed oral effect weakens that immediate action –outcome link but can increase accidental overexposure. A ritualized evening oil can become a contextual cue. A discreet concentrate device can permit repeated use across the day. These are plausible learning consequences of pharmacokinetic form, not deterministic outcomes.

The core lesson of Part II is that exogenous cannabinoids enter a spatially precise endogenous control system with comparatively diffuse timing. THC's partial agonism can have full behavioral importance because CB1 sits at strategic synapses across memory, salience, reward, and motor networks. CBD follows a different pharmacology and has genuine clinical effects at meaningful doses, along with interactions and uncertainty. Route writes the time course; development and prior adaptation determine what that time course meets.

Part III — Development, difference, cognition, and learning Back to TOC

8. Why the same product becomes a different experience Back to TOC

Variation is the expected result

One person feels quiet after cannabis. Another becomes talkative. A third develops panic; a fourth notices little. The variation is not evidence that pharmacology is unknowable. It is what pharmacology predicts when a variable exposure enters heterogeneous bodies and adaptive brains.

At least five layers shape the response. The product layer includes THC, CBD, minor constituents, contaminants, and labeling error. The delivery layer includes route, formulation, speed, and bioavailability. The body layer includes metabolism, sex-related biology, body composition, illness, and other medicines. The brain-history layer includes age, tolerance, genetics, psychiatric liability, sleep, stress, trauma, and learning. The situation layer includes expectation, safety, social meaning, and demands placed on performance.

A compact model is:

$$Y = f(X, B, H, S, t) + \varepsilon,$$

where *Y* is an outcome; *X* is the exposure vector; *B* is current biology; *H* is history; *S* is setting; *t* is time; and *ε* represents unmeasured variation. The function is not presumed linear. A twofold rise in THC dose need not double anxiety. Sleep loss and high THC may interact. Prior tolerance may reduce intoxication but not erase divided-attention errors. The equation is a bookkeeping device, not a validated personal-risk algorithm.

Metabolism and pharmacogenetics

CYP2C9 contributes to THC oxidation. Common genetic variants can alter clearance, and CYP2C19 variation can influence CBD metabolism. Enzyme inhibitors or inducers, liver function, and formulation add further variation. Pharmacogenetics is scientifically credible but not yet a consumer-ready prediction service. A genotype does not specify the dose inhaled, the accuracy of a label, or the state of a person's mind.

Genetic influence also operates upstream. Liability to risk-taking, smoking initiation, ADHD, depression, psychosis, and substance use can affect who begins, how often they use, and what outcomes follow. Genome-wide studies identify shared genetic architecture between cannabis phenotypes and psychiatric traits. Mendelian-randomization analyses have produced evidence compatible with bidirectional relationships between cannabis use and schizophrenia liability, while depending on instruments that may reflect broad behavioral propensity rather than THC exposure alone (Vaucher et al., 2018; Pasman et al., 2018; Levey et al., 2023). Genetics complicates causality; it does not make environment irrelevant.

Expectation and setting are biology in context

Expectation can alter attention, interpretation, and reported effect. In a trusted setting, tachycardia may be dismissed; in a threatening setting, it can be read as catastrophe. Familiar sensory cues can elicit conditioned

anticipation before the drug acts. Social norms influence whether quietness feels peaceful or embarrassing. These are not “imaginary” effects. Expectations recruit real predictive, autonomic, and attentional processes.

Set and setting cannot rescue an excessive exposure or neutralize psychosis vulnerability. Nor should they be used to blame someone for a bad reaction. They explain variance at the margin and interact with pharmacology. The compassionate question after an adverse event is not “Why couldn't you handle it?” but “What combination of dose, state, history, and context produced this transition?”

Tolerance is domain-specific

Repeated users may show less heart-rate change, anxiety, or subjective intoxication at a given exposure. Tolerance can be incomplete and uneven. Laboratory performance may improve relative to an inexperienced person at the same nominal dose because the experienced user anticipates and compensates, yet still remain below their sober performance. Cross-tolerance, withdrawal relief, and learned behavioral strategies contribute. The observation “I function normally” is data about experience, not a controlled comparison.

Prior learning also changes motivation. If cannabis has repeatedly preceded sleep, social ease, food, music, or relief from intrusive memories, cues can acquire value. A person may interpret craving as a direct need for the outcome—“I cannot sleep without it”—rather than as a learned prediction partly created by repetition. Sometimes the original symptom remains severe. Sometimes rebound sleep disruption strengthens the belief. Often both are true.

9. The developing brain: a gradient, not a deadline Back to TOC

There is no twenty-fifth-birthday switch

Human brain development extends through adolescence and young adulthood, but it does not “finish” everywhere at age twenty-five. Different measures follow different courses. Cortical thickness, white-matter microstructure, network segregation, dopaminergic signaling, sleep timing, executive performance, and social role transitions do not converge on one universal endpoint. Some change rapidly in adolescence, some continue through the twenties or longer, and some remain plastic across life. Individuals differ, and measurement choices move apparent peaks (Johnson et al., 2009; Adinoff and Nunes, 2025).

Age twenty-five is best treated as a practical caution band in public communication, not a biological border. A twenty-four-year-old is not categorically immature on Tuesday and complete on Wednesday. Nor does rejecting a magical cutoff imply that developmental timing is irrelevant. Risk can follow a continuous gradient and still justify greater protection earlier in life.

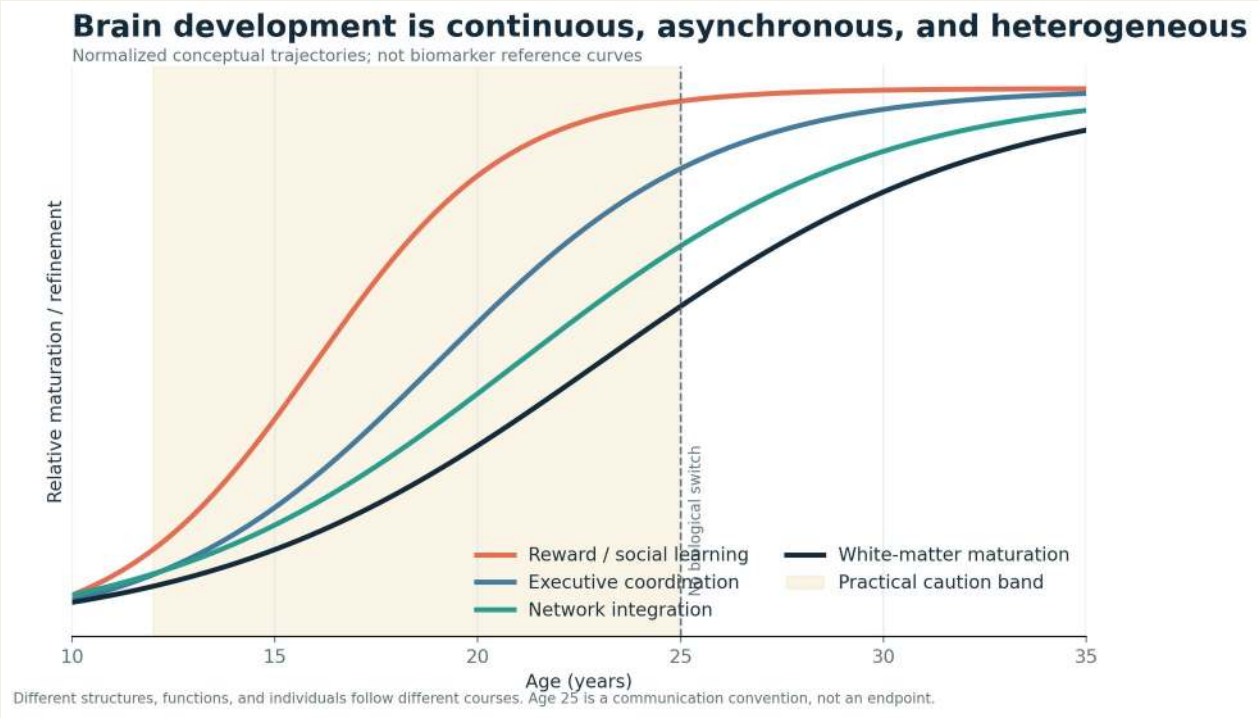

Figure 9. Development is a set of overlapping trajectories, not a countdown to twenty-five. Synaptic remodeling, myelination, network integration, reward learning, cognitive control, and social development follow distinct, heterogeneous paths. The shaded caution band represents uncertainty and ongoing change, not a diagnostic boundary.

Synaptic remodeling and learning-dependent refinement

Development is not simply growth followed by pruning. Synapses are formed, strengthened, weakened, stabilized, and eliminated in region- and cell-specific patterns. Experience helps select which connections persist. “Pruning” is a metaphor for multiple biological processes; it should not imply that the brain cuts away useless material according to a single schedule.

Endocannabinoid signaling participates in neuronal migration, axon guidance, synapse formation, short- and long-term plasticity, and activity-dependent refinement in preclinical models. CB1 receptors appear early and change in distribution across development. This makes a serious mechanistic question unavoidable: what happens when repeated exogenous THC stimulates receptors during a period in which endogenous cannabinoid signals help organize circuits?

The answer is not yet a human causal map. Animal experiments can manipulate timing, dose, sex, and cell type, and some show lasting changes in cognition, social behavior, stress responding, or synaptic function after adolescent cannabinoid exposure. Doses and developmental stages do not translate cleanly. Human adolescents choose exposure within lives that already differ. The careful conclusion is: developmental perturbation is mechanistically plausible, and the hypothesis gains importance from epidemiological signals; a specific irreversible “brain damage” pathway has not been established (Rodrigues et al., 2024; Lichenstein et al., 2022).

Myelination and network coordination

White-matter pathways continue to mature during adolescence and young adulthood. Myelin changes conduction speed and synchrony, while axon caliber, packing, and organization also affect imaging measures. Frontostriatal and frontolimbic networks increasingly support context-sensitive control over action and emotion.

Development is not a contest between an impulsive limbic system and an unfinished prefrontal cortex. Reward, control, memory, and social systems co-develop through reciprocal interactions.

Diffusion MRI studies of young cannabis users report differences in some tracts, but directions and locations vary. Motion, alcohol and nicotine use, premorbid characteristics, scanner choices, and multiple comparisons can influence findings. A difference in fractional anisotropy is not a picture of damaged wiring. It is a statistical signal whose cellular meaning is ambiguous.

Prefrontal and frontostriatal development

Adolescence brings increasing capacity to maintain goals, inhibit prepotent responses, evaluate delayed consequences, and adjust behavior after error. These abilities are already present before adulthood and continue to improve variably. The prefrontal cortex works through networks with striatum, thalamus, hippocampus, amygdala, cingulate, and cerebellum. Repeated intoxication can disrupt learning opportunities even without a permanent lesion. Missed classes, altered peer groups, sleep reversal, and reduced practice of difficult tasks can become developmental mechanisms in their own right.

Frontostriatal systems also learn habits. Early in learning, outcomes strongly govern behavior. With repetition and stable cues, control can shift toward more automatic stimulus–response patterns. This is not unique to cannabis and is not inevitable. But a rapidly relieving or socially rewarded behavior rehearsed across developmental transitions can become embedded while identity and routines are still taking shape.

Hippocampal maturation and memory

Hippocampal subfields and their cortical connections continue to change through adolescence. Relational memory becomes more strategic, and prefrontal systems increasingly guide encoding and retrieval. Acute THC acts directly on a system central to learning while school, vocational training, and social experience are delivering unusually dense streams of information. An exposure need not permanently alter a neuron to matter if it repeatedly interferes with encoding at consequential times.

This observation distinguishes biological and functional persistence. A molecular perturbation may resolve in hours, while the missed learning remains missed. Poor sleep after withdrawal can impair the next day. A lower grade can change course placement. A new peer context can increase future access. Small transient effects can accumulate through feedback.

Reward, social development, and identity

Adolescence and emerging adulthood involve exploration, social reorientation, novelty, status learning, intimacy, and increasing autonomy. Reward sensitivity is context-dependent, not simply elevated. Peer presence can amplify certain risks while also protecting against others. Cannabis can become a badge of belonging, a private refuge, a creative ritual, or an act of self-definition.

Identity matters because behavior is easier to repeat when it becomes a story about the self. “I use sometimes” and “I am a person who needs cannabis to be myself” organize future choices differently. Clinical conversations that attack identity can strengthen defensive commitment. Curiosity about what cannabis is doing *for* someone often opens a more accurate path to discussing what it is also costing.

Stress systems and sleep

Puberty, social evaluation, changing circadian timing, academic demands, and adversity interact with stress regulation. Cannabis can acutely reduce perceived distress for some users, yet high THC can increase anxiety and repeated use can create withdrawal-related dysphoria and insomnia. Sleep loss itself worsens emotional regulation, attention, and psychosis-like experiences. The result can be a loop: distress prompts use, use changes sleep architecture or timing, cessation disrupts sleep, and the disruption is taken as proof that use is indispensable.

The endocannabinoid system participates in stress adaptation. That fact does not determine the sign of repeated exogenous THC's effect. A short-term reduction in arousal and a long-term increase in dependence risk can coexist. Development makes the loop more consequential because coping repertoires and expectations are being learned.

What neuroimaging can and cannot tell us

Structural and functional imaging studies report group differences in prefrontal, hippocampal, striatal, cerebellar, and network measures among adolescent or young adult users. Reviews of roughly ninety or more studies find substantial heterogeneity and no single reproducible lesion signature (Lichenstein et al., 2022; Nosko et al., 2025; Ricci et al., 2026). Earlier literature often relied on small cross-sectional samples, flexible analyses, and imperfect control of alcohol or tobacco.

Prospective large cohorts improve temporal resolution. In a five-year study of 799 adolescents, self-reported cannabis exposure was associated with greater thinning in prefrontal areas enriched for CB1 expression (Albaugh et al., 2021). The finding is important and observational. Cortical thinning is a normal developmental phenomenon with multiple possible cellular bases. The association does not establish that THC destroyed cortex, and it has not established a mechanism for psychosis.

Large datasets also create new pitfalls: small effects can be statistically robust but individually non-predictive; repeated analyses of the same cohort can look like independent replication; baseline abstainers may begin for reasons related to prior brain or behavior. Imaging is strongest when embedded in prospective measurement, preregistration, dose detail, and convergence with behavior—not when a colored cluster is used as a verdict.

10. Cannabis before 25: what we know, what we fear, and what we still do not know Back to TOC

What we know

Earlier initiation is associated with a higher probability of later Cannabis Use Disorder, especially when experimentation becomes weekly or daily use. Frequent adolescent use predicts lower educational attainment and school completion across prospective cohorts. Acute THC impairs learning during a life period in which learning has unusually high downstream leverage. Psychosis-related risk is concentrated in frequent, high-THC patterns and in people with vulnerability. Adolescent brains are undergoing continuing, heterogeneous refinement, and the endocannabinoid system participates in developmental signaling (Leung et al., 2020; Chan et al., 2024; Rodrigues et al., 2024).

These statements differ in causal strength. Acute impairment is experimentally established. The association between early regular use and later CUD is strongly supported but entangled with shared liability. Educational associations are consistent and graded, yet partly attenuate in family-controlled designs. Developmental roles of the endocannabinoid system are mechanistically well established in animals, while the long-term human consequence of adolescent THC exposure remains incompletely specified.

The most defensible warning concerns a pattern, not a birthday: **earlier + repeated + higher-THC exposure**, particularly in the presence of psychiatric symptoms, family history, sleep disruption, trauma, or polysubstance use. A single exposure at seventeen and daily high-potency use from fourteen to twenty-two are not scientifically commensurate.

What we fear

The central fear is not that THC freezes the brain in childhood. It is that repeated pharmacological and behavioral perturbation can alter a developmental trajectory through several small channels that reinforce one another. Acute encoding failures can reduce learning. Use can reorganize time and peers. Tolerance can encourage dose escalation. Withdrawal can make sober periods feel worse. Relief can become a dominant coping strategy. In susceptible systems, high THC can amplify anomalous salience, paranoia, or psychotic symptoms. Each path may be modest; together they can change the state a young person occupies.

This is a Flow Hijacked synthesis, not a proven chain in every user. It is compatible with developmental neuroscience, addiction learning, and longitudinal epidemiology. It should be tested with intensive longitudinal studies that measure product potency, sleep, symptoms, cognition, and social transitions before and after exposure changes.

A second fear is loss of option value. Adolescence and emerging adulthood contain choices whose effects compound: qualifications, apprenticeships, relationships, relocation, and treatment engagement. Frequent intoxication need not cause a permanent cognitive deficit to narrow those options. Conversely, reducing use, treating insomnia, changing peers, or finding safer belonging can restore options. Developmental vulnerability and developmental opportunity are two sides of the same plasticity.

What we still do not know

We do not know a universal safe age, safe frequency, or safe THC concentration. We do not know the long-term effect of many contemporary concentrates because their prevalence postdates the classic cohorts. We lack precise cumulative-dose measurement. We do not know which imaging differences precede use in most participants or which persist after long abstinence. We cannot yet translate polygenic scores into ethically defensible individual advice. Sex-related differences are plausible and sometimes observed, but not stable enough to support simple rules.

We also do not know how much of the educational association is biological intoxication, sleep, peer selection, school disengagement, criminalization, family liability, or reciprocal causation. The fractions likely vary across people and policy contexts. Co-twin studies suggest that shared genetic and family factors explain part of several cognitive and educational associations (Jackson et al., 2016). They do not prove that daily high-potency adolescent exposure is harmless: discordant twins can still differ in nonshared adversity, measurement is coarse, and extreme exposure is uncommon.

Relative risk, absolute risk, and the individual

Risk communication should begin with a baseline. If an outcome occurs in 1 of 100 otherwise similar unexposed people and an exposure doubles risk, the exposed risk is approximately 2 of 100: a 100 percent relative increase and a 1 percentage-point absolute increase. If baseline risk is 10 of 100, the same relative risk corresponds to about 20 of 100 and a 10-point increase. Odds ratios are not risk ratios, especially when outcomes are common, and cannot be converted without a baseline and assumptions.

For psychotic disorder, no single absolute number applies across countries, exposure definitions, ages, follow-up, family history, and potency. The population lifetime probability of a schizophrenia-spectrum disorder is on the order of one percent, while transient psychotic-like experiences are much more common. Daily high-potency use can be associated with several-fold higher odds of first-episode psychosis in case–control data, but that does not mean that most daily users develop schizophrenia or that cannabis explains every case. In a person with high familial or clinical vulnerability, absolute risk could be meaningfully higher than a population average.

For CUD, denominators also matter. A meta-analysis estimated that roughly 22 percent of people who had used cannabis met criteria for CUD across included studies; estimates were higher among younger and regular users, with dependence estimates around one-third in some young regular-use samples (Leung et al., 2020). A recent US estimate found past-year CUD in about 30 percent of past-year users, most mild or moderate (Choi et al., 2024). These are population estimates with changing definitions and survey periods, not a prediction that any given experiment becomes addiction.

A practical scientific conclusion

There is no magical cliff at twenty-five. There is a defensible gradient of caution. Delaying initiation preserves time for learning and circuit refinement and reduces the years available for escalation. Avoiding frequent use and high-THC products matters more than treating all exposure as equal. New paranoia, hallucinations, severe mood elevation, collapsing school function, inability to cut down, or use that has become necessary for sleep or emotional survival are warning signs, not character defects.

For a young person already using, fear-heavy absolutes can backfire when they conflict with lived experience. A better conversation is specific: What product? How much THC? How often? What has changed in sleep, memory, motivation, anxiety, relationships, or control? What happens during a pause? Is use solving a problem that has another treatment? Precision is more credible than catastrophe.

11. Cognition, motivation, education, and recovery Back to TOC

Six clocks of cognitive effect

Claims about “long-term cognitive damage” often combine six time windows. **Acute intoxication** covers the period of direct drug effect. **Residual effect** covers a later interval in which intoxication has faded but performance may not be fully restored. **Withdrawal effect** appears after repeated exposure stops and may be driven by sleep loss, irritability, or craving. **Chronic-use association** compares people with different histories, sometimes without adequate abstinence. **Persistent effect** remains after a verified period sufficient to clear acute and withdrawal influences. **Developmental consequence** includes missed learning and altered life opportunities even if laboratory performance later recovers.

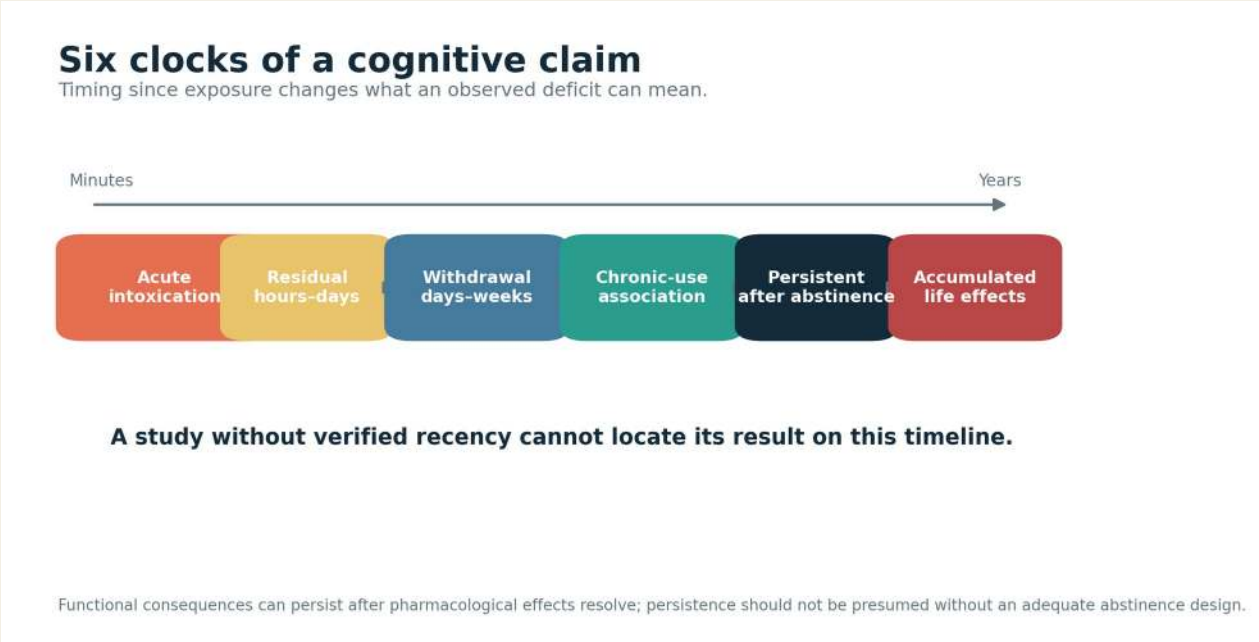

Figure 10. Cognitive effects by time window. Acute, residual, withdrawal-related, chronic-associated, persistent, and accumulated functional effects answer different questions. Studies that do not verify recency cannot locate an observed deficit on this timeline.

Acute THC impairment of episodic learning, working memory, attention, processing speed, inhibitory control, and psychomotor performance is supported by controlled experiments and reviews. Effect sizes differ by dose and task. Verbal learning and immediate memory are among the more reliable domains. Complex divided-attention and driving-related tasks remain important even when simple reaction time appears intact (Broyd et al., 2016).

Working memory and episodic memory

Working memory is a temporary workspace, not a storage box. It keeps goals and intermediate results active while distractions compete. THC can reduce precision and increase susceptibility to interference. In episodic learning, the largest problem is often acquisition: less information is effectively encoded. A later recall deficit may therefore reflect poor registration, not accelerated forgetting of an intact trace.

This distinction has practical meaning. Re-reading while intoxicated can create familiarity without durable learning. A conversation may feel coherent while details fail to bind. A learner can compensate by slowing down, but compensation consumes capacity and may fail under stress. Frequent exposure timed to evening study or morning classes can produce a functional pattern larger than a single test effect.

Attention, inhibition, and decision-making

Sustained attention requires monitoring over time; divided attention requires managing simultaneous demands; inhibition requires suppressing a dominant response; decision-making integrates values, uncertainty, and delay. THC can affect each, but no task is process-pure. Slower responding may improve accuracy in one experiment and create a real-world hazard in another. Experienced users may adopt compensatory caution while missing unexpected events.

Laboratory risk-taking findings are mixed. Cannabis does not reliably transform everyone into a reckless decision-maker. Acute impairment can instead make updating noisier, narrow attention, or increase reliance on salient immediate cues. Motivation is similarly resistant to a slogan. The stereotype of “amotivational syndrome”

confounds intoxication, depression, poverty, school disengagement, and selection. Experimental and longitudinal evidence suggests possible alterations in reward processing and effort in some heavy users, but not a universal destruction of ambition (Skumlien et al., 2021).

What meta-analysis finds

Scott and colleagues' 2018 meta-analysis combined 69 studies with 2,152 frequent or heavy adolescent and young-adult users and 6,575 comparison participants. The overall cognitive association was small, approximately standardized mean difference −0.25. Importantly, in studies requiring more than 72 hours of abstinence, the average association shrank to about −0.08 and was not statistically significant. Publication bias and study quality also influenced estimates (Scott et al., 2018).

The result rules out two slogans. It does not support “cannabis destroys cognition” as a universal large effect. It also does not support “there is no cognitive concern.” A small average can contain more substantial effects in heavy, early-onset, or vulnerable subgroups. Seventy-two hours may remove much acute and residual effect but not all withdrawal or stored-metabolite concerns. The moderator was not a randomized abstinence experiment. And educational consequences can persist even when a neuropsychological score improves.

Meta-analysis also inherits the exposure weakness of its studies. “Frequent use” can mean different frequencies, potencies, routes, and durations. A cohort using lower-potency flower decades ago cannot completely answer a question about contemporary concentrates. Better estimates require milligram-level or biomarker-informed exposure, repeated cognition, and baseline measurement before initiation.

Abstinence and recovery

Recovery is domain- and person-specific. Acute effects resolve as drug action wanes. Residual effects commonly improve over hours to days. Withdrawal-related sleep disruption can transiently worsen attention. Meta-analyses and monitored-abstinence studies often show improvement over days to weeks, especially in verbal learning. CB1 receptor availability can substantially normalize over a similar period in small PET samples.

Persistent deficits are harder to establish. Some long-term cohorts report decline associated with persistent heavy use, while twin and sibling comparisons attenuate many associations. Premorbid cognitive differences, education, tobacco, other drugs, and attrition matter. The most honest synthesis is that many average cognitive differences are small and at least partly reversible, while persistent heavy exposure beginning early may carry greater risk and is not adequately represented by “ever use.” No study can promise complete recovery for every exposure history; none justifies telling every user that permanent brain damage has occurred.

Education is not an IQ test

Adolescent cannabis use predicts school noncompletion, lower qualifications, and reduced educational attainment in pooled longitudinal cohorts, with stronger associations at higher frequency (Chan et al., 2024). Causality is mixed. Early conduct problems, family adversity, peer networks, tobacco and alcohol, mental illness, and prior disengagement predict both cannabis use and educational outcomes. School exclusion or criminal penalties can also mediate harm.

Yet residual confounding does not make the association meaningless. Intoxication during instruction, impaired encoding, changed routines, sleep disruption, and dependence are plausible causal routes. Education can also

affect use by changing peers and opportunity. The system is reciprocal. A useful intervention may need to address tutoring, sleep, anxiety, belonging, and substance use together.

Motivation without contempt

When a person seems “unmotivated,” several mechanisms may be hiding under one judgment. Depression can reduce reward anticipation. ADHD can make delayed goals hard to sustain. Cannabis can provide immediate, reliable relief or interest. Withdrawal can make ordinary rewards temporarily flat. Repeated easy reward can reduce willingness to tolerate boredom. Social environments can stop offering credible alternatives. None is laziness as an essence.

Flow Hijacked interpretation: a behavior becomes dominant when its predicted value is repeatedly confirmed at short horizons while slower rewards remain uncertain. The relevant comparison is not cannabis versus an abstract healthy life; it is cannabis now versus the options the person expects to work. Treatment becomes stronger when it builds believable competing paths rather than merely subtracting the drug.

The developmental synthesis

The developing brain is neither glass nor stone. It is plastic, robust, heterogeneous, and vulnerable precisely because it learns. THC can acutely impair functions central to that learning. Repeated early use is associated with CUD, educational, cognitive, and psychiatric risks, especially at high frequency and potency. Shared liability explains part, not necessarily all, of those patterns. Many measured cognitive effects improve with abstinence; missed experiences and established habits may require active repair.

The appropriate message is therefore neither “wait until the brain is finished at twenty-five” nor “age is just propaganda.” It is: delay gives a developing system more time and reduces cumulative opportunity for escalation; frequency and THC exposure matter; vulnerability is uneven; recovery is common enough to support hope; uncertainty is large enough to require humility.

Part IV — Psychosis, mood, dependence, and the learned need Back to TOC

12. Psychosis: neither universal cause nor irrelevant bystander Back to TOC

Four phenomena that must be separated

An intoxicated person can briefly misinterpret a sound and retain insight. Another can experience intense paranoia, hearing or seeing things others do not, or disorganized thought. A third can meet criteria for cannabis-induced psychotic disorder, with symptoms clinically prominent beyond an ordinary intoxication. A fourth can develop a schizophrenia-spectrum illness with persistent or recurrent psychosis, negative symptoms, and functional decline. These phenomena overlap but are not synonyms.

THC can produce transient psychotic-like symptoms in placebo-controlled experiments. That is established causal evidence for an acute effect. Cannabis use precedes psychotic disorder in many longitudinal studies, with higher associations at greater frequency. High-potency daily use is associated with particularly high odds in case–control studies. Cannabis-induced psychosis has a substantial transition rate to schizophrenia-spectrum diagnosis. Continued use after first-episode psychosis predicts relapse. No one design settles every bias, but the convergence is stronger than a single correlation (Hindley et al., 2020; Marconi et al., 2016; Di Forti et al., 2019; Murrie et al., 2020; Schoeler et al., 2016).

The boundary conditions are equally important. Cannabis is not necessary for schizophrenia: many patients have never used it. It is not sufficient: most people who use cannabis, including frequently, do not develop schizophrenia. Schizophrenia is heterogeneous and influenced by many genetic and environmental factors. The defensible model is that THC can act as one causal-risk component—precipitating, amplifying, or advancing illness in some susceptible systems.

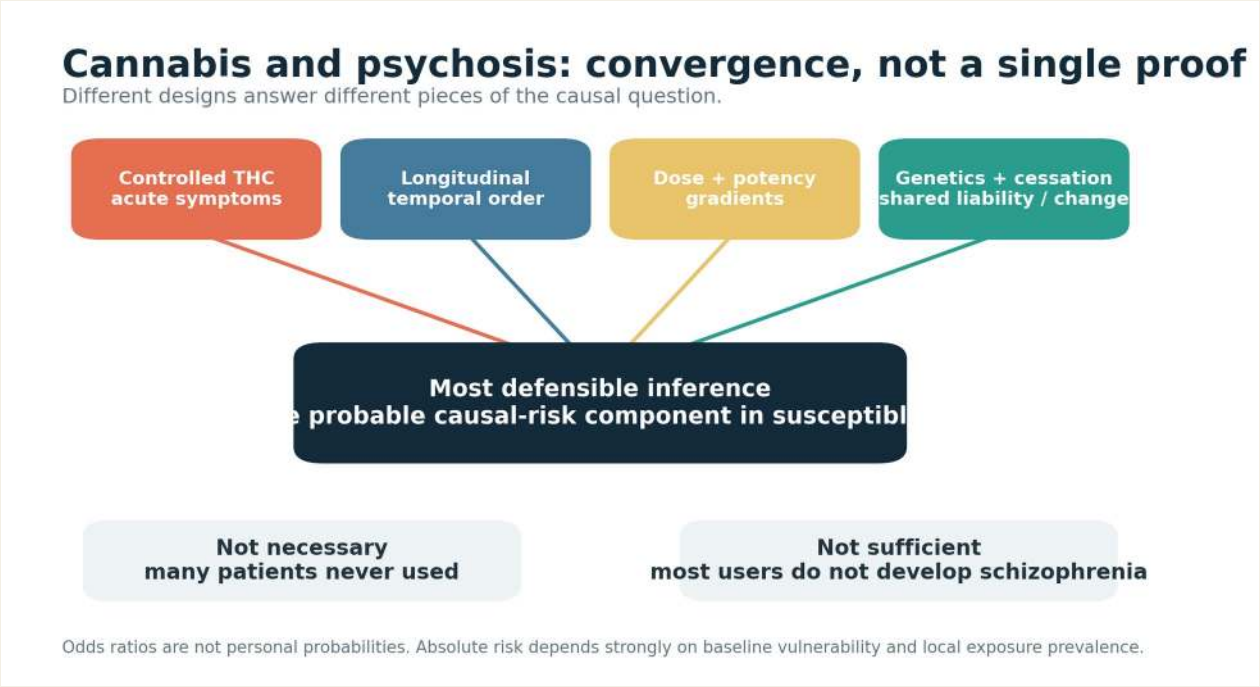

Figure 11. Triangulating cannabis and psychosis. Controlled THC challenge establishes acute symptom potential; longitudinal timing and dose-response support prediction; high-potency and cessation patterns add specificity; genetics demonstrates shared liability and possible bidirectionality. No arrow means that cannabis is necessary or sufficient for schizophrenia.

The experimental bridge

In controlled administration studies, THC increases total, positive, and negative psychosis-like symptom ratings relative to placebo, with substantial average standardized effects in meta-analysis of 15 studies and 331 participants (Hindley et al., 2020). Symptoms are usually transient in screened adults. Experiments establish that THC can cause a psychotomimetic state; they do not reproduce years of developmental exposure or diagnose schizophrenia.

Paranoia may emerge through altered salience, anxiety, anomalous experiences, impaired working memory, and uncertainty about other people's intentions. Dopamine is relevant but not a single switch. THC's CB1 effects can modify GABAergic and glutamatergic control of midbrain dopamine neurons; recent synthesis suggests points of convergence between cannabis exposure and psychosis-related dopamine dysfunction (Ahrens et al., 2025). The route from receptor to delusion is networked and conditional.

Dose-response, frequency, and potency

A 2016 meta-analysis of ten studies found that the heaviest cannabis-use category was associated with an odds ratio of 3.90 for psychosis-related outcomes compared with nonuse (95 percent confidence interval 2.84–5.34) (Marconi et al., 2016). Categories differed across studies, and an odds ratio is not an absolute probability. The gradient nevertheless argues against a simple explanation based only on ever having tried cannabis.

In the EU-GEI multicentre case–control study, 901 people with first-episode psychotic disorder and 1,237 controls were recruited across eleven European and Brazilian sites. Compared with never use, daily use was associated with adjusted odds of 3.2, and daily use of locally defined high-potency cannabis with odds of 4.8 (Di Forti et al., 2019). Product potency was inferred from local market types and self-report, not chemically assayed for each

event. Recall, selection, and residual confounding remain. The magnitude, dose pattern, and consistency with acute THC effects make the result clinically serious without making it a personal prediction.

EU-GEI estimated population-attributable fractions of 20.4 percent for daily use and 12.2 percent for high-potency use across sites, with larger site-specific estimates. A PAF asks what fraction of cases might not occur under a counterfactual removal of an exposure if the model and causal assumptions hold. It is not the probability that cannabis caused a particular person's psychosis. It also depends on local prevalence: the same relative effect produces a larger population burden where exposure is common.

Potency-specific evidence is strongest for psychosis and CUD, but still imperfect. “High potency” has meant different thresholds, contemporary concentrates are not well represented in older cohorts, and frequency correlates with potency preference. Yet it would be equally mistaken to treat a high-THC concentrate as epidemiologically interchangeable with low-potency flower. THC is the acute psychotomimetic constituent, and delivered dose belongs inside the causal model.

Age of onset and bringing illness forward

Among people who develop psychosis, cannabis use has been associated with onset about 2.7 years earlier in a meta-analysis of 83 studies and 8,167 participants (Large et al., 2011). Earlier presentation could reflect precipitation in a vulnerable person, greater surveillance, other substances, or prodromal changes that promote use. The finding is compatible with cannabis bringing forward illness that might otherwise have appeared later, while not proving that every affected individual would eventually have become ill.

This “component cause” model matters clinically. Advancing psychosis by several years can interrupt education, work, and relationships during a pivotal period even if lifetime incidence were unchanged. For some people, cannabis may contribute to an episode that would not otherwise have occurred. Population data cannot identify which counterfactual applies to an individual.

Cannabis-induced psychosis and transition

Cannabis-induced psychotic disorder is not automatically a transient, closed event. A 2020 meta-analysis estimated transition to schizophrenia after cannabis-induced psychosis at approximately 34 percent, higher than for several other substance-induced psychoses (Murrie et al., 2020). Registry estimates vary with follow-up, diagnostic practice, and population, sometimes closer to one in five. Transition is not inevitable, and the diagnosis may sometimes reveal an emerging primary disorder rather than create it.

The clinically correct response is therefore neither reassurance that “it was only the cannabis” nor fatalism that schizophrenia is certain. It is follow-up, reduction of exposure, sleep stabilization, assessment of other substances and mood symptoms, family engagement when appropriate, and rapid access to early-psychosis care. Persistent hallucinations, delusions, severe confusion, inability to sleep, dangerous behavior, or marked functional change warrant urgent assessment.

Genetics and reverse causation

Schizophrenia is highly polygenic. The same genetic and developmental liabilities can influence sensation seeking, social difficulty, distress, and likelihood of cannabis initiation. Mendelian-randomization studies often find a stronger and more consistent direction from schizophrenia liability toward cannabis initiation, while some also support a cannabis-to-schizophrenia direction (Gage et al., 2017; Vaucher et al., 2018; Pasman et al., 2018).

Instruments based on lifetime use may capture general behavioral liability and do not model daily high-potency exposure well.

In a large analysis of EU-GEI and UK Biobank, schizophrenia polygenic risk and heavy cannabis use contributed independently; a multiplicative interaction was not detected. In EU-GEI, daily high-potency use remained associated with first-episode psychosis after adjustment for the score, with an odds ratio about 5.09 (Austin-Zimmerman et al., 2024). Failure to detect interaction does not show that vulnerability is irrelevant. Interaction depends on statistical scale, power, score portability, and exposure measurement. Family history and prior symptoms remain clinically useful even when a current polygenic score is not.

Continued use, cessation, and prognosis

Among people with first-episode psychosis, continued cannabis use is associated with higher relapse, hospitalization, and poorer adherence; more frequent and potent patterns appear worse. People who stop tend to have better trajectories, although illness severity and social stability can influence both stopping and outcome (Schoeler et al., 2016).

One 2025 EU-GEI analysis found that odds of psychotic disorder approached those of never-users after roughly 37 weeks since cessation, with more persistent elevation among some frequent high-potency users (Bond et al., 2025). This is encouraging and preliminary. Recall of stopping, survivor bias, and retrospective design prevent using thirty-seven weeks as a recovery promise. The robust message is simpler: continued exposure after psychosis is a modifiable risk marker, and reduction deserves support rather than shame.

13. Anxiety, depression, bipolarity, and suicide are different questions Back to TOC

Anxiety and panic

Acute THC can provoke anxiety and panic, especially at higher doses, in unfamiliar settings, or in people with prior sensitivity. This causal acute effect should not be confused with whether cannabis creates a chronic anxiety disorder. Prospective studies show small or inconsistent associations with later anxiety after adjustment, and self-medication is substantial (Xue et al., 2021; Beletsky et al., 2024).

Different anxiety conditions may relate differently to use. Social anxiety can motivate use before interaction. Panic can be triggered by bodily sensations during intoxication. Generalized anxiety can precede nightly use and worsen during withdrawal. PTSD-related hyperarousal or nightmares can motivate relief-seeking. A study that combines these phenotypes loses mechanism.

CBD is not a settled answer. Small acute studies at large doses have produced anxiolytic signals, but controlled clinical evidence is sparse and heterogeneous. THC-containing products can worsen anxiety. Consumer products may deliver far less CBD than trials and may include THC. A person whose anxiety improves immediately can still develop a reinforcement loop; a person whose panic begins with THC has direct reason to avoid further exposure.

Depression

Adolescent cannabis use is associated with later depression in prospective meta-analysis. Gobbi and colleagues combined eleven studies with 23,317 participants and estimated an odds ratio of 1.37 for depression in young adulthood (Gobbi et al., 2019). That is a modest relative association, not proof that cannabis caused each

episode. Premorbid mood symptoms, adversity, family factors, tobacco, alcohol, and disengagement can confound it. Depressive symptoms can also increase subsequent use.

Mechanisms can operate in both directions. Intoxication can provide temporary distance from rumination. Frequent use can disrupt routine or sleep, increase avoidance, and generate conflict. Withdrawal can produce dysphoria. Reduced opportunity can worsen mood. Conversely, an untreated depressive course can drive escalating self-medication. The clinical unit is a loop, not a one-way arrow.

Bipolar spectrum and mania

Cannabis use and CUD are associated with manic symptoms, bipolar onset, worse course, hospitalization, and recurrence in observational reviews. Some pooled estimates are in the two- to threefold range, but study quality and heterogeneity limit causal precision (Gibbs et al., 2015; Maggu et al., 2023; Sorkhou et al., 2024). Impulsivity, sleep loss, reward sensitivity, and other substance use can precede both cannabis use and mania. People may use during prodromal elevation because sensation seeking and confidence have already risen.

THC-related sleep disruption, salience, and psychotomimetic effects make caution particularly important in someone with bipolar disorder or prior mania. New reduced need for sleep, pressured speech, grandiosity, agitation, risky behavior, or psychosis requires timely clinical evaluation. Cannabis should not be assumed to be the sole cause; it should not be dismissed as irrelevant.

Suicidal ideation and attempts

Cannabis use and CUD are associated with suicidal ideation and attempts across several populations. In the adolescent-use meta-analysis, estimated odds were 1.50 for suicidal ideation and 3.46 for suicide attempt in young adulthood (Gobbi et al., 2019). The attempt estimate concerned a rarer outcome and is vulnerable to residual confounding and imprecision. Depression, trauma, impulsivity, pain, social adversity, and polysubstance use can drive both exposure and risk.

The evidence does not establish a simple direct pathway from cannabis to suicide. It does establish that heavy use or CUD in a suicidal person is clinically relevant. Intoxication can impair judgment; withdrawal can worsen sleep and mood; combined alcohol use can increase disinhibition. Asking directly about intent, plan, access to means, and protective supports is more useful than debating one attributable cause. Immediate suicidal intent is an emergency regardless of causal story.

Psychiatric hospitalization

Emergency visits and hospitalization can follow panic, severe intoxication, vomiting, psychosis, mania, injury, or combined-substance exposure. Administrative data show rising cannabis-related encounters in some legalizing markets, especially involving high-potency products and edibles, but coding and surveillance change over time. A diagnosis recorded with cannabis does not prove cannabis caused the entire admission. It does identify a product and use pattern worth specifying.

The psychiatric synthesis is asymmetric. Evidence is strongest for acute psychotic-like symptoms and for a contributory relationship with psychotic disorder under frequent high-THC exposure. It is more mixed for chronic anxiety and depression, while bipolar-course and suicidality associations deserve clinical attention without simple causal claims. “Mental health” is too broad a box.

14. Cannabis Use Disorder: when an option becomes a governing loop Back to TOC

Addiction is possible, common enough to matter, and not inevitable

Cannabis can be addictive. Denying this requires ignoring tolerance, a reproducible withdrawal syndrome, craving, repeated failed attempts to cut down, use despite consequences, and the lives of people who seek treatment. Claiming that everyone who uses becomes addicted is equally false. Risk is distributed and strongly related to frequency, age of onset, product strength, vulnerability, and context.

The DSM-5-TR diagnosis of Cannabis Use Disorder is based on at least two of eleven criteria occurring within twelve months. The criteria cover use in larger amounts or for longer than intended; unsuccessful efforts to reduce; substantial time spent obtaining, using, or recovering; craving; failure in major roles; social or interpersonal problems; abandonment of activities; hazardous use; continued use despite physical or psychological harm; tolerance; and withdrawal. Two or three criteria indicate mild, four or five moderate, and six or more severe disorder.

The count is not a moral score. Tolerance and withdrawal alone can occur during appropriately supervised medical treatment and do not automatically imply addiction. Legal trouble is not a diagnostic criterion, appropriately separating a disorder from policy. Functional context matters: a criterion should represent a clinically meaningful pattern, not disagreement with a person's values.

How common?

No single percentage answers “How addictive is cannabis?” The denominator may be everyone who ever tried it, past-year users, weekly users, daily users, adolescents, or treatment-seeking adults. Diagnostic systems also changed.

A 2020 systematic review estimated pooled CUD prevalence of roughly 22 percent among people who had used cannabis, with risk rising strongly among regular and daily users; dependence estimates reached roughly one-third in some cohorts of young regular users (Leung et al., 2020). In recent nationally representative US data, about 30.3 percent of past-year users met past-year CUD criteria: 16.9 percent mild, 8.4 percent moderate, and 5.0 percent severe (Choi et al., 2024). The latter is not a lifetime probability of transition after one trial and should not be exported unchanged to every country or product market.

These estimates undermine both rhetorical extremes. Most people who ever use cannabis do not develop severe CUD. Among current frequent users, clinically significant symptoms are not rare. A population can have lower average dependence liability per exposure than nicotine and still carry substantial burden because use is common.

Withdrawal is a syndrome, not a rumor

Cannabis withdrawal commonly begins within twenty-four to forty-eight hours after stopping heavy or regular use, often peaks around days two through six, and improves over one to two weeks. Sleep disturbance and vivid dreams can persist longer. Irritability, anger, anxiety, restlessness, decreased appetite, dysphoria, headache, sweating, abdominal discomfort, and craving vary in intensity. The syndrome is usually not medically dangerous in isolation, but it can be profoundly disruptive and can trigger relapse (Connor et al., 2022).

Bahji and colleagues synthesized 47 studies with 23,518 participants and estimated withdrawal prevalence around 47 percent, with much higher prevalence in inpatient or treatment samples than population samples (Bahji et al., 2020). Heterogeneity was large. Tobacco withdrawal, baseline insomnia, and psychiatric symptoms can overlap. The right inference is that withdrawal is common after regular or dependent use, not that every user experiences it.

Dream intensity has a comprehensible basis. THC can alter sleep architecture, and frequent users may experience REM-related changes. On cessation, rebound vivid dreaming can occur alongside insomnia. A person who began using for sleep may then encounter several bad nights when stopping and conclude that natural sleep is impossible. The conclusion can be learned during withdrawal even when sleep would later improve.

Neuroadaptation without reductionism

Repeated THC exposure changes CB1 signaling. Receptors can desensitize and become less available; endogenous tone and downstream pathways adapt. Human PET studies show lower cortical CB1 availability in daily users with substantial reversal during abstinence. These changes support tolerance and withdrawal, but a receptor image does not diagnose CUD. Some daily users have adaptation without impaired control; some people with severe impairment are driven by powerful learning and environment not visible on PET.

Reward findings are also nuanced. Acute THC can increase mesolimbic dopamine indirectly. In chronic heavy users, some imaging studies find blunted dopamine synthesis capacity or release and reduced response to non-drug rewards. This could reflect adaptation, premorbid difference, tobacco, stress, or comorbidity. It does not establish a permanently “depleted dopamine system.” A blunted response can recover and can coexist with strong cue-triggered motivation.

Stress systems become more relevant as use shifts from positive reinforcement—seeking pleasure—to negative reinforcement—escaping discomfort. The person may no longer be pursuing a dramatic high. They may be using to feel ordinary, to sleep, to eat, or to silence withdrawal and anxiety. That transition is central to addiction and frequently invisible to outsiders.

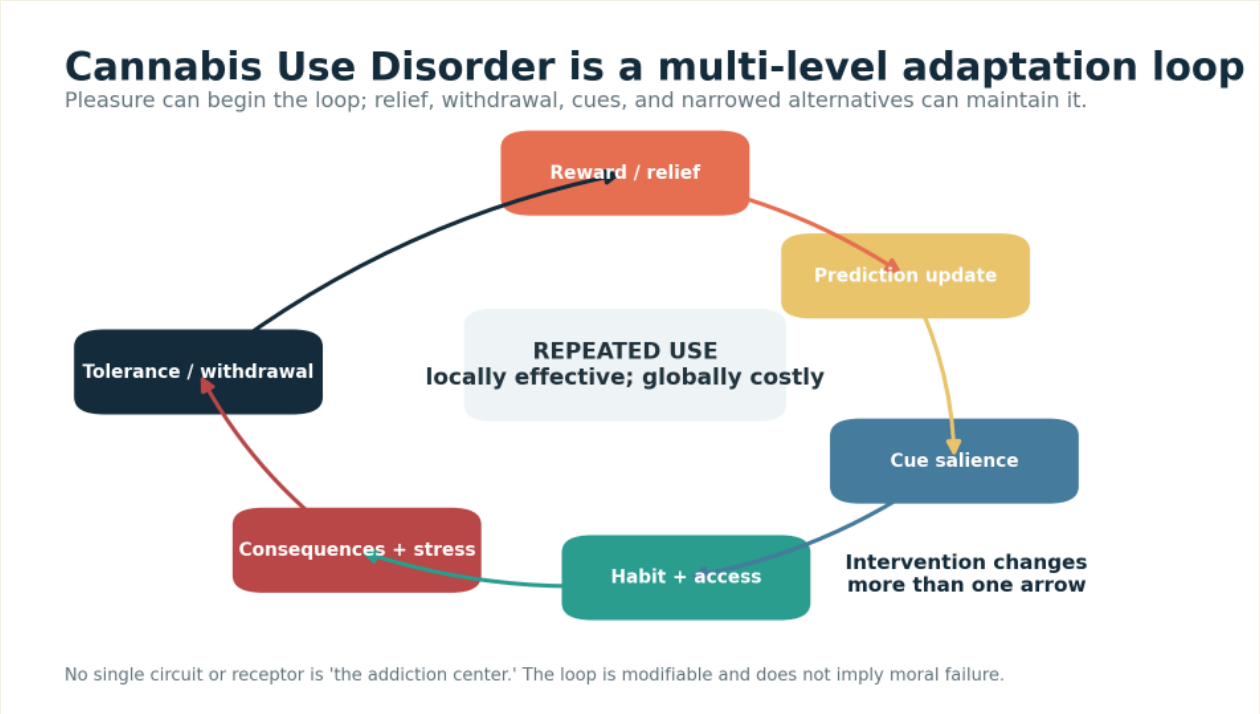

Figure 12. A multi-level Cannabis Use Disorder loop. Rapid reward or relief updates predictions; cues gain salience; tolerance and withdrawal change the sober baseline; habits reduce deliberation; consequences increase stress; a narrowed environment makes the same behavior more valuable. No single node is "the addiction center," and every arrow is potentially modifiable.

Cue learning, prediction, and habit

Suppose cannabis repeatedly follows the end of work and precedes relief. The room, time, device, friends, music, and bodily tension become predictors. In temporal-difference language, the expected value of a state can be updated by a reward-prediction error:

$$\delta_t = r_t + \gamma V(s_{t+1}) - V(s_t),$$

$$V(s_t) \leftarrow V(s_t) + \alpha \delta_t.$$

Here r_t is immediate reward or relief, γ discounts the future, and α is a learning rate. This standard reinforcement-learning equation is an analogy and modeling framework, not evidence that a person's CUD is literally governed by one scalar value. It clarifies why reliable immediate relief can outweigh delayed, uncertain costs.

As repetition continues, behavior can become less sensitive to current outcome value and more controlled by cues. Habit does not mean mindless or immutable. It means that initiation requires less deliberation. Stress, alcohol, loneliness, or the sight of a familiar object can retrieve the sequence before a conscious decision feels present.

Craving is not only desire for pleasure. It can be a prediction that something is missing, an attentional capture, a bodily urge, or a plan becoming dominant. Trying to suppress it can paradoxically keep the cue active. Effective care therefore works with cues, routines, alternative rewards, distress tolerance, sleep, and social context—not only with information about harm.

Potency, early onset, and frequency

Frequency is the most consistent exposure-level predictor of CUD. Daily access rehearses cues, accelerates tolerance, and makes withdrawal more likely. Earlier regular use extends cumulative exposure and occurs during a period of identity formation and high social learning. High-THC products can strengthen acute reward, anxiety, tolerance, and withdrawal, and systematic reviews increasingly associate potency with CUD symptoms, although product-specific longitudinal evidence remains thinner than frequency evidence (Petrilli et al., 2022; Lake et al., 2025).

No threshold guarantees dependence. Risk can rise continuously. A high-potency product used rarely may not create the same cumulative adaptation as lower-potency cannabis used throughout every day. The exposure vector must stay intact.

The Flow Hijacked model of CUD

In a dynamical picture, a person's behavior moves through a state space shaped by sleep, stress, cues, access, relationships, mood, and drug state. Repetition can deepen an attractor basin around use: more starting states now flow toward the same action. Withdrawal tilts the landscape by making non-use temporarily aversive. Consequences can remove competing activities and deepen the basin further.

This is a Flow Hijacked interpretation. Attractors are mathematical objects in models; no scan has located a “cannabis attractor” in the brain. The value of the metaphor is relational. It explains why willpower at one instant is a weak lever against a landscape built across months, and why changing sleep, access, peers, cues, treatment, and daily structure can reshape the landscape. An attractor is not a prison.

Treatment and recovery

Motivational enhancement therapy, cognitive-behavioral therapy, and contingency management have the strongest psychosocial evidence, often with better results when combined. Effects are modest, engagement varies, and relapse is common. Treatment can aim at abstinence or meaningful reduction depending on severity, safety, and goals. For someone with psychosis, pregnancy, severe cardiovascular disease, or repeated dangerous intoxication, the safety case for stopping is stronger.

No medication is currently approved specifically for CUD. Trials of cannabinoid agonists, N-acetylcysteine, gabapentin, antidepressants, and other agents have not produced sufficiently reliable benefit for routine pharmacotherapy, though research continues (Nielsen et al., 2019; Spiga et al., 2025). Symptom-targeted care may still address sleep, anxiety, depression, ADHD, pain, or withdrawal under clinical supervision.

Recovery is not disproved by craving or recurrence. Relapse can reveal a high-risk state or missing support. Reducing exposure can improve sleep after an initial difficult interval, restore time, lower tolerance, and reopen activities. People recover through many routes: formal treatment, mutual support, family, changed environment, purpose, medication for co-occurring illness, or self-directed change. The scientific point is agency within an adaptive system.

15. Self-medication: when relief and worsening coexist Back to TOC

The immediate effect can be real

People commonly report using cannabis for pain, insomnia, anxiety, trauma-related distress, low mood, nausea, loneliness, or emotional overload. Dismissing all relief as illusion is both inaccurate and clinically destructive. THC can reduce pain unpleasantness, promote sleep onset for some, alter threat attention, and create psychological distance. Ritual and expectation add real contextual effects. CBD or standardized products may have indication-specific benefits.

Immediate benefit does not answer the long-term question. A treatment can relieve a symptom tonight while increasing tolerance, dependence, impairment, or avoidance over months. Conversely, a risk does not mean there was never benefit. The task is to compare time horizons and alternatives.

Negative reinforcement

When use removes an aversive state, removal reinforces the behavior. This is negative reinforcement, not punishment and not “negative” in a moral sense. If evening anxiety falls soon after inhalation, the association is learned efficiently. If anxiety returns during withdrawal, repetition is reinforced twice: cannabis relieves the original distress and the new distress partly generated by adaptation.

Pain creates a similar challenge. Cannabis may modestly reduce symptoms while sedation decreases movement, work, or rehabilitation. Or it may permit function and reduce another medicine. Individual trajectories differ. A useful assessment asks not only “Did it help pain?” but “What happened to mobility, sleep, cognition, dose, mood, and daily life over time?”

Trauma-related use can narrow experiential avoidance in the short term. If intoxication becomes the only route away from memories or hyperarousal, opportunities to learn that distress can be tolerated or processed may shrink. This is a plausible learning account, not an accusation that a person chose avoidance. The original suffering remains clinically primary.

The counterfactual treatment question

Self-medication is often compared with nothing. The relevant comparison may be trauma-focused therapy, pain rehabilitation, insomnia treatment, antidepressant care, a safer antiseizure medicine, housing support, or a less intoxicating cannabinoid formulation. Access and prior treatment failure matter. A person may choose cannabis because available alternatives were unaffordable, stigmatizing, ineffective, or dangerous.

That context should change care, not evidence standards. A report of relief supports the claim that relief was experienced. It does not establish that a product treats a disorder in randomized trials. Likewise, weak trial evidence does not erase an individual's response; it limits confidence about attribution and generalization.

A compassionate inventory

A scientifically useful inventory has two columns. The first asks what cannabis gives: relief, pleasure, sleep, connection, identity, appetite, interruption of thought. The second asks what it takes: memory, money, time, lungs, motivation, relationships, driving safety, emotional range, or control. Both columns can be populated. Change becomes possible when the function of use is understood well enough to replace it rather than merely condemn it.

The central fact of CUD is not weak character. It is that an adaptive system learned a locally effective answer so repeatedly that the answer began to govern the questions. Treatment is the work of making other answers credible again.

Part V — The body, the road, reproduction, and manufactured uncertainty Back to TOC

16. Respiratory, cardiovascular, gastrointestinal, sleep, and reproductive health Back to TOC

Smoke is a route, not a cannabinoid

Burning cannabis produces a chemically complex aerosol containing fine particles, carbon monoxide, polycyclic aromatic hydrocarbons, aldehydes, and airway irritants. Deep inhalation and breath-holding can increase deposition. The most consistent long-term respiratory associations are cough, sputum production, wheeze, and bronchitic symptoms; symptoms often improve after stopping (Ghasemiesfe et al., 2018; NASEM, 2017).

Evidence for fixed airflow obstruction, COPD, and lung cancer from cannabis alone is less settled than it is for tobacco. Many users also smoke tobacco, cumulative cannabis exposure is measured poorly, cohorts historically contained relatively few very heavy cannabis-only smokers, and inhalation patterns differ. Recent large tobacco-adjusted studies report associations with asthma and COPD, while spirometric and cancer findings remain inconsistent (Kaplan et al., 2021; Rustagi et al., 2026). “Not proven to cause lung cancer” is not “clean for the lungs.”

Vaporization can lower exposure to products created by combustion but introduces device, temperature, solvent, flavorant, and contaminant questions. An aerosol is not water vapor. High-temperature degradation and small-particle deposition remain relevant. Route-specific evidence should not be used to transfer a pulmonary harm from smoke to a purified oral medicine—or to erase the systemic THC risk of a vaporized product.

Cardiovascular physiology and events

Acute THC commonly raises heart rate, can alter blood pressure, and may cause orthostatic dizziness. Sympathetic activation, reduced parasympathetic influence, vasodilation, increased myocardial oxygen demand, and carboxyhemoglobin from smoke provide plausible pathways to acute events, especially in people with coronary disease. Tolerance modifies some effects (Page et al., 2020).

Recent observational syntheses associate cannabis use with acute coronary syndrome, stroke, and cardiovascular mortality. A 2025 meta-analysis covering twenty-four studies and nearly 200 million observations estimated relative risks around 1.29 for acute coronary syndrome, 1.20 for stroke, and 2.10 for cardiovascular mortality (Storck et al., 2025). Those impressive denominators largely come from administrative or population data, not precise product-level exposure. Tobacco, stimulants, socioeconomic risk, diagnosis coding, and reverse causation remain. Earlier meta-analysis was less conclusive.

The correct interpretation is a cardiovascular safety signal with uncertain causal magnitude, not a settled event rate. Acute chest pain, fainting, severe palpitations, or neurological deficit after cannabis should not be dismissed as anxiety. Risk is plausibly greater with rapid high THC, smoke, underlying heart disease, and co-use of stimulants. CBD products can also interact with cardiovascular medicines through metabolism even without intoxication.

Cannabinoid hyperemesis syndrome

Cannabinoid hyperemesis syndrome, or CHS, is a recurrent syndrome of severe nausea, vomiting, and abdominal pain associated with prolonged frequent cannabis exposure. Hot bathing often provides temporary relief, though it is not unique to CHS. Patients may cycle through emergency departments, dehydration, electrolyte disturbance, and extensive testing before the pattern is recognized (Sorensen et al., 2017; Senderovich et al., 2021).

The apparent paradox—an antiemetic-associated drug linked to vomiting—does not invalidate the diagnosis. Dose, chronic adaptation, gut and central CB1 signaling, stress responses, gastric motility, and individual susceptibility may differ across acute and chronic exposure. Mechanism and incidence remain uncertain. There is no definitive diagnostic biomarker, and cyclic vomiting syndrome, pregnancy, obstruction, infection, metabolic disease, and other causes must be considered.

Acute care can include fluids, electrolyte correction, antiemetics, and clinician-directed therapies; sustained cessation is the most reliable preventive intervention. Symptom resolution after stopping and recurrence after resumption strengthen the inference. Telling a distressed patient that “cannabis cannot cause vomiting because it treats nausea” delays useful care.

Gastrointestinal function and appetite

THC can stimulate appetite and alter nausea, motility, and visceral sensation. These effects support certain medical uses and can also produce dry mouth, constipation, or changes in eating patterns. The gastrointestinal endocannabinoid system participates in motility, secretion, inflammation, and brain–gut signaling, but broad wellness claims outrun clinical evidence. A receptor role does not establish that chronic exogenous stimulation improves regulation.

Sleep: sedation is not identical to restoration

Some people fall asleep faster after THC. In chronic-pain trials, cannabinoids produce small average improvements in self-reported sleep. Primary insomnia trials are few, short, and heterogeneous, and objective sleep measures do not consistently track perceived benefit (AminiLari et al., 2022).

THC can alter REM sleep and sleep architecture. Tolerance to sedating effects can develop. Frequent use may shift sleep timing or pair sleep onset with a drug cue. Stopping can cause insomnia and vivid dreams, which reinforces resumption. CBD can be alerting or sedating depending on dose, context, and other medicines. Therefore “cannabis helps sleep” can be true as a report of tonight and uncertain or false as a claim about durable sleep health.

Sleep also modifies every other risk domain. Insufficient sleep worsens memory, emotion regulation, reaction time, and psychosis vulnerability. A product that shortens sleep onset but produces late dosing, morning impairment, or dependence may have a different total effect from one that improves pain and enables consolidated sleep. Trials should measure function, not only minutes to unconsciousness.

Reproductive health

Studies of semen report associations between frequent cannabis exposure and sperm concentration, motility, morphology, or epigenetic marks, but results are inconsistent and frequently confounded by tobacco, abstinence interval, illness, and selection (Payne et al., 2019; Srinivasan et al., 2021; Cameron et al., 2025). Human evidence

does not support a simple claim that cannabis reliably lowers testosterone or causes infertility. Absence of a simple hormonal result does not establish reproductive safety.

Female reproductive evidence is also limited. Endocannabinoid signaling participates in ovulation, implantation, and pregnancy biology, yet effects of external cannabis on time to pregnancy and fertility are not consistently quantified. People planning pregnancy have reason to discuss use and medications with a clinician because the evidence is uncertain and exposure can extend into early unrecognized pregnancy.

17. Pregnancy, fetal exposure, and breastfeeding Back to TOC

Two patients, one exposure, many confounders

THC crosses the placenta. THC and CBD can enter breast milk. The fetal or infant exposure depends on maternal dose, route, frequency, timing, metabolism, formulation, placental biology, feeding pattern, and time since use. Lipophilicity can prolong presence in milk. No consumer label can translate these variables into a verified safe fetal dose (Metz and Borgelt, 2018; Monfort et al., 2022).

Pregnancy research is ethically constrained: randomized exposure trials are impossible. Observational comparisons face unusually strong confounding. Cannabis use during pregnancy correlates with tobacco and alcohol, nausea, pain, psychiatric symptoms, trauma, poverty, nutrition, prenatal-care access, and partner use. Self-report can be suppressed by stigma or punitive policy. Potency and trimester are often missing.

These limitations require causal humility, not indifference. Updated synthesis of roughly fifty-one studies and more than twenty-one million pregnancies found prenatal cannabis exposure associated with low birth weight (approximate odds ratio 1.75), preterm birth (1.52), and small-for-gestational-age birth (1.57) after study-level adjustment, with a smaller and less certain association with perinatal mortality (about 1.29) (Lo et al., 2024; updated 2025). Adjustment quality varied and residual confounding remains, but the direction is concerning.

Longer-term development

Studies of children exposed prenatally report the most consistent signals in attention, behavior, and executive function, while global cognition, language, and motor findings are heterogeneous (Sorkhou et al., 2024; Domingues et al., 2026). Maternal genetics and mental health, postnatal environment, tobacco, and exposure measurement complicate attribution. Newer cohorts face a changed potency market.

No evidence supports a deterministic statement that prenatal exposure produces a particular disability. No high-quality evidence establishes a safe dose, route, or trimester. Professional guidance therefore applies a precautionary recommendation to avoid cannabis and use evidence-based alternatives for nausea, pain, sleep, or psychiatric symptoms (ACOG, 2025).

Care without punishment

Screening should be a supportive conversation, not a trap. Punitive policies can deter prenatal care and honest disclosure, thereby worsening health. A pregnant person using cannabis for hyperemesis, trauma, pain, or withdrawal needs an alternative plan. Simply saying “stop” without treating the function of use can leave severe symptoms or drive concealment.

Breastfeeding decisions require the same compassion. Current guidance advises avoiding cannabis during lactation because transfer occurs and infant neurodevelopmental safety is not established. Clinical support

should weigh feeding, maternal health, treatment options, and exposure reduction without pretending that uncertainty is zero risk or certain harm.

18. Cannabis and driving Back to TOC

Impairment is a systems task

Driving demands continuous visual sampling, divided attention, lane control, speed regulation, prediction of other road users, motor timing, and rapid response to rare events. THC can impair each component. A driver may compensate by slowing down or increasing following distance, but compensation does not restore the ability to detect every hazard. Unexpected events reveal deficits that a predictable simulator can miss (Simmons et al., 2022; Metrik et al., 2026).

Experimental studies support acute impairment in lateral control, reaction time, divided attention, and composite driving performance. Epidemiological estimates of collision risk vary. A classic meta-analysis of nine observational studies estimated odds around 1.92 for serious or fatal collision after recent use, with high heterogeneity and challenges in controlling alcohol and time since exposure (Asbridge et al., 2012). Later estimates differ with design. The exact multiplier is less secure than the existence of acute impairment.

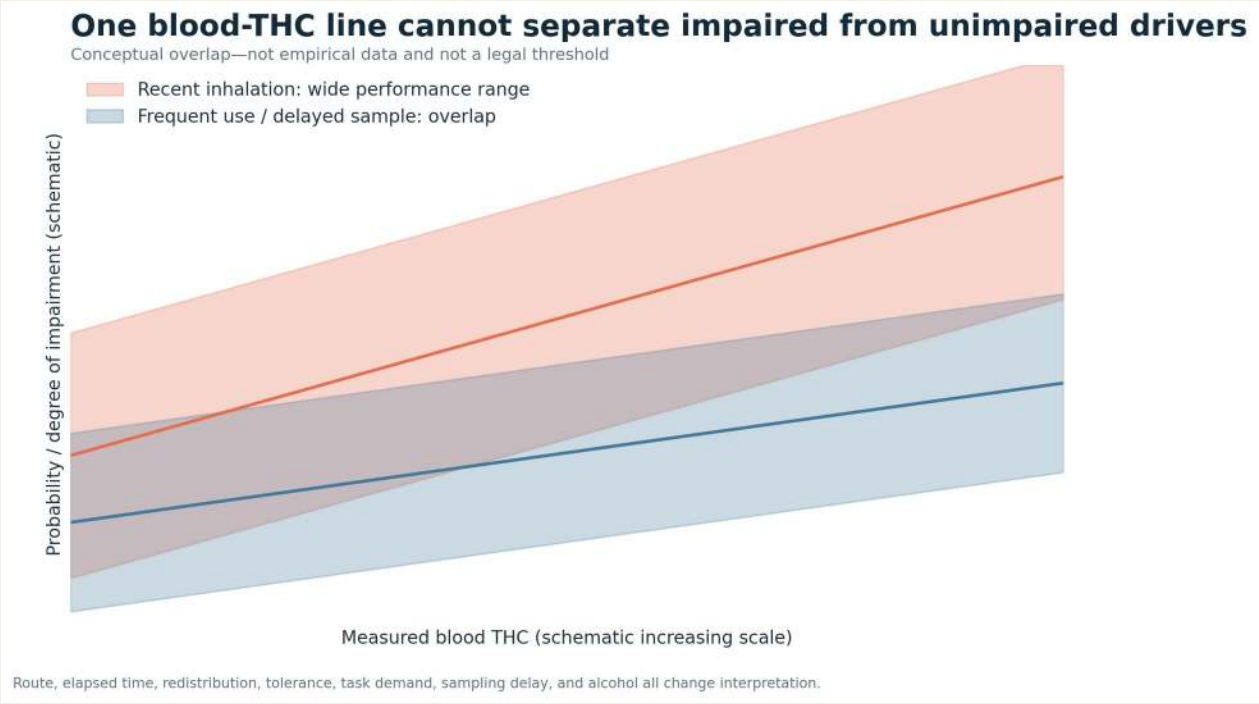

Figure 13. Why blood THC is not a breath-alcohol analogue. Route, sampling delay, rapid redistribution, tolerance, residual detection, task demand, and combined substances intervene between concentration and performance. A concentration contributes evidence but does not identify an individual's impairment with one universal line.

Blood THC and the failed simple threshold

Blood alcohol concentration maps to impairment imperfectly but predictably enough for population rules. THC behaves differently. Inhalation produces a rapid peak followed by a steep fall during continuing intoxication. Oral use produces a delayed, broader course. Frequent users can have detectable baseline THC. Sampling usually occurs long after driving. Serum and whole-blood values differ.

A 2025 systematic review found that most included studies did not show a dependable linear relationship between measured blood THC and driving outcomes (Behzad et al., 2025). This does not mean concentration is irrelevant. A very high value obtained promptly after an event can support recent exposure. It means a universal per-se threshold will misclassify some impaired and some non-impaired people. Observed behavior, timing, route, toxicology, field assessment, and other substances form a better evidential whole.

Alcohol changes the equation

Alcohol plus THC produces greater impairment than either alone across many tasks, sometimes additive and sometimes more-than-additive. People can be below a legal alcohol limit and still be substantially impaired by the combination. Controlled driving research also shows why delayed oral THC can overlap unexpectedly with alcohol (Simmons et al., 2022; Metrik et al., 2026).

CBD does not restore driving ability after THC. Sedating medicines, sleep deprivation, and illness can compound risk. A person should not drive, cycle in traffic, operate machinery, or supervise hazardous activity while impaired. Fixed waiting periods are unreliable across dose and route; oral effects can last much longer than expected. The educational principle is to plan transport before exposure and not use subjective confidence as a clearance test.

19. High-potency products, synthetic cannabinoid receptor agonists, and contaminants Back to TOC

Concentration changes the margin for error

High-potency flower and concentrates permit larger THC delivery with less material and often faster administration. This can steepen the effective dose curve, increase acute anxiety and cognitive disruption, accelerate tolerance, and make withdrawal or CUD more likely. Psychosis evidence is the most consistent potency-specific psychiatric signal. Emergency presentations involving severe intoxication, vomiting, and pediatric ingestion can also increase where concentrated edibles or extracts are common.

Product categories remain crude. A concentrate can be used in a small amount; a lower-potency product can be used repeatedly. Labels may report total THC that includes potential THC after decarboxylation, or distinguish Δ9-THC imperfectly. Risk communication should describe concentration as an enabling variable, not a complete dose.

Synthetic cannabinoid receptor agonists are not stronger cannabis

Products sold under names such as Spice or K2 have contained diverse synthetic cannabinoid receptor agonists, or SCRAs, sprayed onto plant material or incorporated into liquids. Many are high-potency, high-efficacy or full CB1 agonists, unlike partial-agonist THC. Some have active metabolites, non-CB1 targets, steep dose-response, or long duration. Product composition can change between packets and within one packet (Sholler et al., 2020).

This pharmacology produces a different toxicological category. Agitation, severe psychosis, seizures, hyperthermia, cardiovascular instability, acute kidney injury, coma, and death are reported. Comparative emergency data find more severe neuropsychiatric and cardiovascular toxicity than ordinary cannabis (Zaurova et al., 2016; Mosca et al., 2025). Routine cannabinoid screens may not detect new compounds.

The label “synthetic cannabis” therefore obscures mechanism. The products are not standardized replicas of the plant. They are unpredictable receptor-active chemicals with different efficacy and toxicity. This book provides no synthesis, preparation, or acquisition information.

Delta-8, semi-synthetic, and novel cannabinoids

Commercial markets increasingly contain Δ8-THC, hexahydrocannabinol, THC-O-related products, and other semi-synthetic or converted cannabinoids. Some occur naturally only in trace amounts and are manufactured through chemical conversion. Human pharmacology, impurity profiles, and labeling are often poorly characterized. A 2025 controlled crossover study found Δ8-THC intoxicating, although generally less potent per dose than Δ9-THC; this does not establish safety across unregulated products (Spindle et al., 2025).

Legal status or hemp origin does not answer toxicology. Reaction by-products, residual reagents, incorrect isomer assignment, and unknown dose add manufacturing risk. “Novel” should be read as “less studied,” not “improved.”

Contaminants and label accuracy

Cannabis can carry pesticides, metals, molds, bacteria, and residual solvents. The plant can accumulate metals from soil; extraction can concentrate both desired and undesired chemicals. Immunocompromised users may be especially vulnerable to microbial contamination. Detection does not always imply a clinically meaningful dose, and prevalence varies by jurisdiction, but standards and enforcement differ widely (Dryburgh et al., 2018; Jameson et al., 2022).

CBD-market testing repeatedly finds products with substantially more or less cannabinoid than labeled, including undeclared THC. Pharmaceutical products manufactured under regulatory controls should not be generalized from this evidence. The distinction is part of the therapeutic chapter: standardized formulation is not cosmetic; it is a condition of interpretable efficacy and safety.

20. Interactions with alcohol, nicotine, and medicines Back to TOC

Pharmacodynamic and pharmacokinetic interaction

A pharmacodynamic interaction occurs when compounds affect the same function—for example, THC and alcohol both impair driving. A pharmacokinetic interaction occurs when one changes another's absorption, metabolism, or elimination. The first can occur without a blood-level change; the second may be silent until toxicity or treatment failure appears.

Alcohol has the clearest functional interaction. Combined use worsens psychomotor performance, lane control, and judgment. Alcohol can also alter THC absorption depending on timing. Nicotine and cannabis are commonly co-used, sometimes in the same product. Tobacco confounds respiratory and psychiatric research and can create a second dependence. One drug's cue can trigger the other.

Benzodiazepines, sedating antihistamines, gabapentinoids, opioids, and some antipsychotics can add to sedation, dizziness, and psychomotor impairment. Cannabis is not a reliable protection against opioid overdose. Co-use with stimulants can increase tachycardia, blood pressure, anxiety, and cardiac demand. Evidence is strongest for alcohol; for many medication pairs, concern rests on pharmacology and case evidence rather than dedicated trials.

CBD and enzyme-mediated interactions

At pharmaceutical exposure, CBD inhibits several metabolic pathways and can meaningfully raise concentrations of co-medications. The best-established example is clobazam: CBD increases its active metabolite, *N*-desmethylclobazam, contributing to somnolence. With valproate, CBD increases the risk of transaminase elevations even when valproate concentrations do not rise proportionally (Morrison et al., 2019; FDA, 2023).

Potential interactions involve CYP2C19, CYP3A4, CYP2C9, UGT enzymes, and transporters. In-vitro inhibition lists are hypothesis generators, not proof that every listed medicine has a clinically important interaction. Dose matters. A few milligrams of uncertain consumer CBD and 1,000 mg/day purified CBD should not receive the same interaction table. Conversely, a consumer can take enough concentrated CBD to matter.

Antiepileptic drugs, warfarin and other narrow-therapeutic-index medicines, immunosuppressants, and some antidepressants or antipsychotics deserve clinician or pharmacist review. THC and CBD can also cause effects—anxiety, orthostasis, sedation—that are mistaken for a primary illness or medication failure. Sudden changes in cannabis use can change an interaction state.

A safer clinical question

“Does cannabis interact with my medication?” is too broad for a yes-or-no answer. The answer needs the exact cannabinoid product, labeled and plausible dose, route, frequency, medication, indication, liver function, and symptoms. People should not abruptly stop essential medicines based on an interaction list. The scientific aim is medication reconciliation, monitoring, and substitution where warranted—not alarm by database.

Part VI — Medicines, vulnerability, state space, and the frontier Back to TOC

21. Therapeutic cannabinoids: one label, unequal evidence Back to TOC

"Medical cannabis" is not one intervention

A therapeutic claim must name a molecule or characterized mixture, formulation, dose, route, indication, comparator, and outcome. "Medical cannabis works" is as scientifically incomplete as "psychiatric medicine works." Purified oral CBD, dronabinol, nabilone, nabiximols, vaporized flower, and an artisanal oil differ in chemistry and evidence. Authorization by a jurisdiction is not the same as regulatory proof of efficacy.

Evidence is classified here as strong or established, moderate, limited, inconclusive, negative, or inadequately studied. The label applies to a specific indication–product pair. It is not transferable to recreational safety or another disease. Benefits and adverse effects belong in the same sentence.

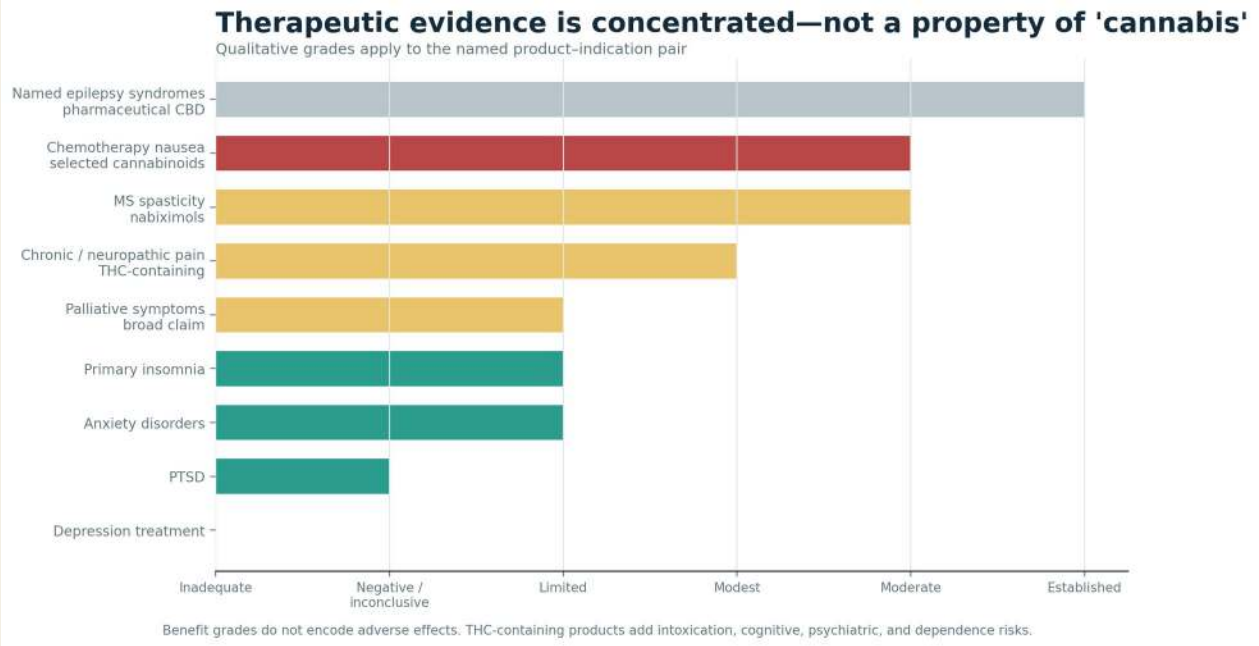

Figure 14. Therapeutic evidence by indication and formulation. Strong evidence is concentrated in purified pharmaceutical CBD for named epilepsy syndromes. Moderate evidence supports selected standardized THC-containing products for chemotherapy-related nausea, MS spasticity, and some chronic pain, usually with small benefits and more adverse effects. Anxiety, PTSD, primary insomnia, and broad palliative claims remain limited or inconclusive.

Established: purified CBD for named epilepsy syndromes

Multiple phase III trials show that purified pharmaceutical CBD, added to other therapy, reduces seizures in Dravet syndrome, Lennox–Gastaut syndrome, and tuberous sclerosis complex (Devinsky et al., 2017; Devinsky et al., 2018; Thiele et al., 2018; Thiele et al., 2021). This is the strongest cannabinoid therapeutic evidence.

It is narrow in the scientific sense. The trials do not establish CBD for every epilepsy, low-dose retail CBD, or whole-plant cannabis. Treatment uses standardized weight-based dosing and clinical monitoring. Somnolence,

diarrhea, reduced appetite, and liver-enzyme elevation occur. Clobazam and valproate interactions matter. An effective medicine can require caution; that is what makes it medicine rather than a wellness symbol.

Moderate: chemotherapy-induced nausea and vomiting

Dronabinol and nabilone reduced chemotherapy-related nausea and vomiting compared with placebo or some older antiemetics in trials, but much evidence predates modern antiemetic regimens. Psychoactive and neurological adverse effects are common. Contemporary randomized evidence suggests that standardized oral THC/CBD extract can help refractory symptoms as an adjunct (Grimison et al., 2024). Guidelines generally place cannabinoids after established antiemetic options or in selected refractory cases, not as a universal first line.

The distinction between chemotherapy-related nausea and ordinary nausea is important. A benefit in one setting does not negate CHS or support cannabis for every gastrointestinal complaint. Indication determines the counterfactual.

Moderate: multiple-sclerosis spasticity

A Cochrane review of twenty-five randomized trials concluded that nabiximols and related cannabis-based medicines probably improve patient-reported spasticity over the short term, while objective measures are less consistent and neurological or psychiatric adverse events increase (Filippini et al., 2022). Nabiximols is a standardized approximately 1:1 THC:CBD oromucosal spray, not an interchangeable dispensary category.

Patient-reported improvement matters; spasticity is experienced, not only measured. Unblinding from psychoactive effects can inflate subjective differences, and most trials are short. Moderate evidence means a reasonable option for selected patients, not a large or risk-free effect.

Moderate but modest: chronic and neuropathic pain

Living systematic reviews find small short-term reductions in chronic pain intensity from some THC-containing or balanced products, particularly in neuropathic pain. Functional improvement is smaller or uncertain, and dizziness, sedation, nausea, and cognitive effects increase (AHRQ, 2025; Wang et al., 2021). Evidence for high-CBD products alone is weaker.

Average effects are easy to miscommunicate. A small mean difference can hide meaningful responders and nonresponders. Enriched-enrolment designs, expectancy, and unblinding can magnify apparent benefit. Short trials cannot adequately measure tolerance, CUD, cardiovascular events, or long-term function. Opioid-sparing claims remain uncertain; ecological reductions in prescribing do not prove that cannabinoids safely substitute for opioids in individuals.

Limited: palliative care and cancer symptoms

Cannabinoids are used for pain, appetite, sleep, nausea, and distress in serious illness, where patient goals and risk tolerance may differ. Yet a systematic review spanning fifty-two studies, including twenty randomized trials and 4,786 participants, found no dependable broad improvement in palliative symptoms or quality of life (Doppen et al., 2022). Older appetite trials found megestrol more effective than dronabinol in cancer-related anorexia.

Inconclusive population evidence is compatible with individualized use when options are exhausted. It does not justify a general claim that cannabis treats cancer or improves survival. Laboratory antitumor effects at selected

concentrations are not clinical oncology evidence, and substituting cannabis for effective cancer treatment is dangerous.

Limited and condition-dependent: sleep

Cannabinoids may slightly improve self-reported sleep among people with chronic pain. Evidence for primary insomnia is sparse. THC can shorten sleep latency for some users while altering architecture, producing tolerance, next-day effects, and rebound insomnia on cessation. A sedative sensation is not proof of restorative sleep. Trials need objective sleep, daytime function, dependence, and follow-up.

Limited or not established: anxiety, PTSD, and psychosis

CBD has preliminary anxiety signals, often at hundreds of milligrams, but trials are small and heterogeneous. A 2026 meta-analysis of fifty-four randomized trials involving 2,477 participants did not find significant cannabinoid benefit for anxiety disorders, PTSD, psychotic disorders, or opioid use disorder, and found no qualifying depression trials (Wilson et al., 2026). This is a sobering update to promotional narratives.

For PTSD, observational reports of improved sleep or nightmares are vulnerable to selection and expectancy; controlled evidence does not show reliable improvement in overall symptoms. THC can worsen anxiety, cognition, and psychosis risk. For psychosis, an individual adjunctive CBD trial showed a modest signal, but pooled evidence remains unclear; consumer CBD is not an antipsychotic treatment (McGuire et al., 2018; Di Francesco et al., 2026).

A therapeutic evidence rule

The closer a product is to a characterized drug—known composition, stable formulation, reproducible dose, indication-specific trial, adverse-event monitoring—the more interpretable its evidence becomes. Whole-plant complexity is not inherently bad, but it makes attribution and replication harder. The burden of proof rises when composition varies.

22. Vulnerability is a distribution, not a type of person Back to TOC

Baseline risk changes absolute risk

Risk is layered. Family history of psychosis, prior psychotic-like experiences, bipolar disorder, severe anxiety reactions, early trauma, ADHD, impulsivity, insomnia, cardiovascular disease, pregnancy, and polysubstance use can alter the relevant baseline or route to harm. None is a prophecy. Most people with a vulnerability factor will not experience every outcome; some adverse outcomes occur without recognized factors.

A useful risk model separates *susceptibility* from *exposure*. Someone with low measured susceptibility can increase risk through daily high-THC use. Someone with strong familial liability can experience meaningful absolute risk from an exposure that appears modest at population level. In a logistic model,

$$\mathrm{logit}[\mathrm{P}(\mathrm{Y}{=}1)] = \beta_0 + \beta_1 \mathrm{X} + \beta_2 \mathrm{V} + \beta_3 (\mathrm{X}{\times}\mathrm{V}),$$

where *X* is exposure and *V* vulnerability. The interaction term may be zero on the multiplicative odds scale even while absolute risk differences vary greatly because baseline probability differs. Statistical noninteraction is not clinical invulnerability.

Family and personal psychiatric history

A first-degree family history of schizophrenia-spectrum or bipolar disorder raises concern because baseline liability is higher. It does not allow a clinician to calculate a precise cannabis-attributable probability. Prior hallucinations, severe paranoia, mania, or cannabis-induced psychosis are more immediate warnings. Continued use after psychosis predicts worse outcomes, making avoidance of THC a high-priority modifiable factor.

Anxiety history predicts neither guaranteed panic nor safety. A past high-dose panic reaction is informative within the person. Depression and trauma can motivate use and increase risk through self-medication. Assessment should trace temporal order: which symptoms existed before use, what changes during intoxication, what changes during withdrawal, and what persists during sustained reduction?

ADHD, impulsivity, and executive control

ADHD is associated with earlier substance initiation and greater CUD risk through impulsivity, reward delay, emotional dysregulation, school difficulty, and shared genetics. Cannabis can feel calming while impairing attention and learning. That subjective response does not diagnose ADHD or demonstrate treatment. Effective ADHD care, structure, and sleep can reduce the problem cannabis is being asked to solve.

Trauma and social context

Trauma can change stress reactivity, threat prediction, sleep, and access to safe relationships. Cannabis may offer rapid distance from unbearable states. Adversity also confounds associations with psychiatric outcomes. Treating trauma as only a statistical nuisance would be ethically and scientifically wrong; it is part of the causal system.

Housing instability, criminalization, discrimination, marketing, product access, peer norms, and opportunity shape exposure and consequences. The same frequency may carry different functional costs in different environments. Social explanation does not erase pharmacology, and pharmacology does not erase social structure.

Sleep and polysubstance use

Sleep loss increases cognitive errors, emotional reactivity, and anomalous experiences. It can both prompt cannabis use and amplify its adverse effects. Alcohol adds impairment; nicotine adds dependence and respiratory burden; stimulants add cardiovascular and psychiatric strain; sedatives add somnolence. Many studies label these “confounders,” but in real lives they are often interacting exposures.

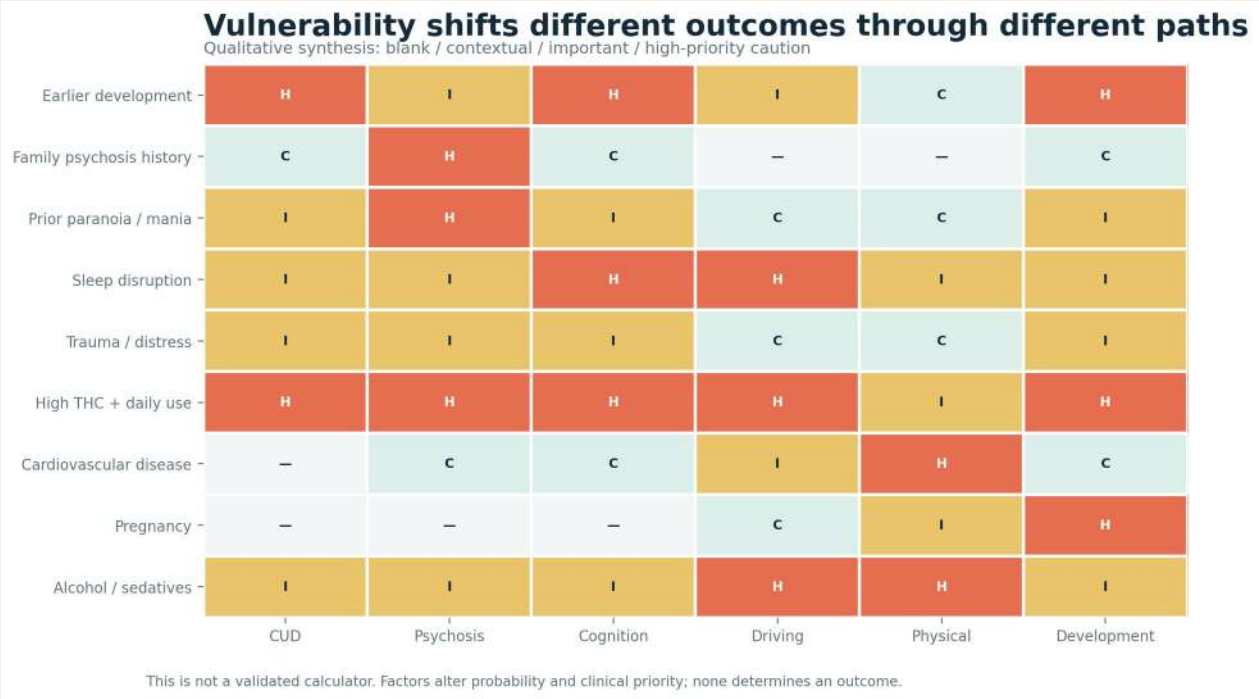

Figure 15. Vulnerability matrix. Developmental timing, psychiatric liability, sleep, trauma, cardiovascular state, product potency, frequency, route, and co-use alter different outcomes. Factors shift probability; they do not sort people into safe and doomed categories.

23. Flow Hijacked: cannabis in a nonlinear, adaptive brain Back to TOC

State space and trajectories

A state space represents the possible configurations of a system using selected variables. For cannabis, a simplified state might include arousal, mood, salience, working-memory stability, craving, sleep pressure, intoxication, and social safety. A trajectory is the system's path through that space. The variables are abstractions; the brain's true dimensionality is vastly greater.

The same perturbation can produce different trajectories because initial conditions differ. A moderate THC exposure after sleep, food, and safety may move one system into relaxation and then back toward baseline. The same nominal exposure during sleep deprivation and emerging paranoia may cross a boundary into panic or psychosis. Nonlinearity means that effect is not necessarily proportional to dose and that interactions can matter more near thresholds.

Metastability

Healthy brain function is neither rigid stability nor random switching. Networks form transient coalitions suited to a task, persist long enough to function, and dissolve when conditions change. This metastability supports flexible movement among attention, memory, exploration, and rest. THC can alter coupling and timing across networks, producing both unusual association and reduced control (Kelso, 2012).

Calling an intoxicated state “metastable” does not explain it by itself. The term earns value only when it generates measurable predictions—for example, altered dwell times, transition probabilities, or network integration under controlled exposure. Human imaging provides suggestive network findings but not a complete dynamical account.

Attractor landscapes

An attractor is a state or set of states toward which a dynamical system tends to evolve. Addiction can be pictured as a landscape in which many combinations of stress, cue, time, and mood flow toward use. Repetition, withdrawal, and loss of competing rewards deepen that basin. Treatment can reshape the landscape by changing access, cues, sleep, social connection, expected relief, and alternative reward (Koob and Volkow, 2016; Le Foll et al., 2024).

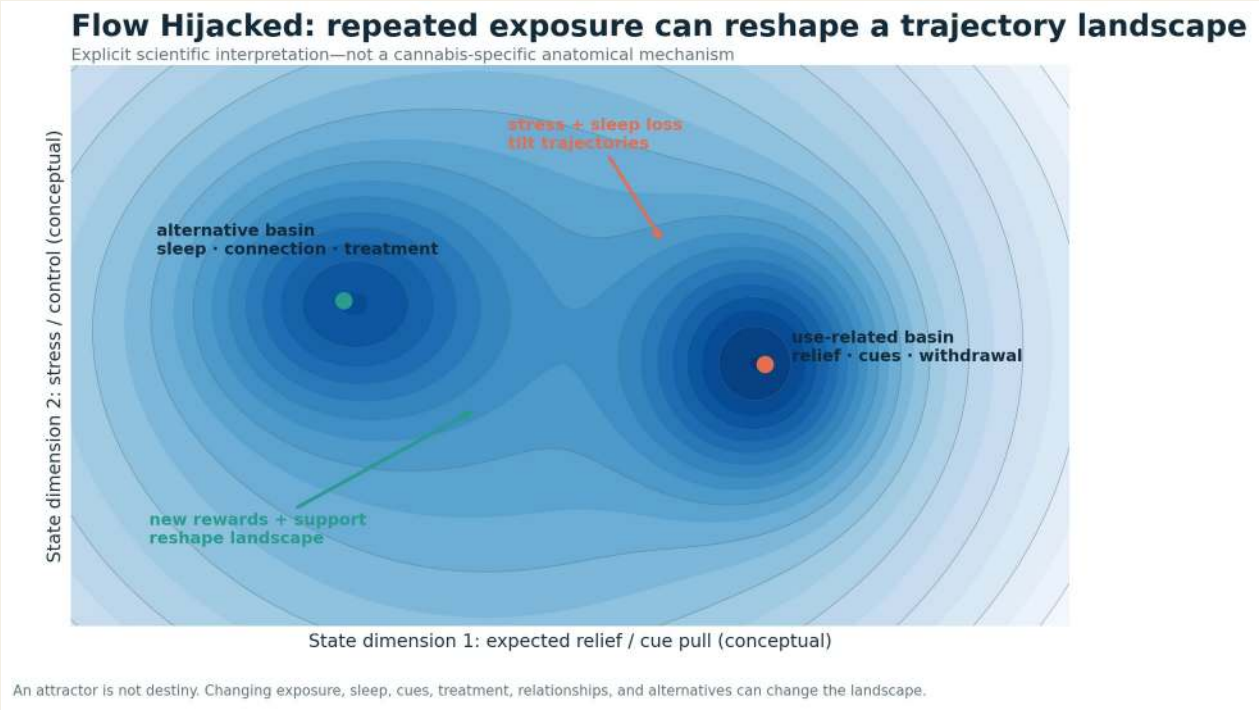

Figure 16. Flow Hijacked state-space model. Repeated high-value relief can deepen a use-related basin; stress and sleep loss tilt the landscape; high THC can create a larger perturbation; treatment and alternative rewards can flatten the basin and open new trajectories. This is an explicit scientific interpretation, not an established cannabis-specific anatomical mechanism.

Prediction and precision

Predictive-processing accounts describe perception and action as inference under uncertainty. A brain estimates causes of sensation and weights prediction errors by expected precision (Friston, 2010). THC-related salience changes could alter how much confidence is assigned to internal thoughts, bodily signals, or ambiguous social cues. A benign coincidence may feel charged with meaning. This is compatible with psychotomimetic experience but remains a theoretical synthesis; no clinical assay currently measures a person's "precision weighting" well enough to predict a reaction.

For self-medication, the brain may predict that distress is intolerable without cannabis and that use will reliably remove it. Repeated confirmation increases confidence; in reinforcement-learning language, actions followed by reliable relief acquire value (Sutton and Barto, 2018). Withdrawal can supply new evidence for the prediction. A testable future model would combine momentary stress, cue exposure, craving, use, relief, and delayed cost in intensive longitudinal data. It should outperform simpler frequency measures before claiming clinical value.

Nonlinear vulnerability

Threshold concepts explain why group averages can coexist with rare severe reactions. Let a latent stability variable z depend on baseline vulnerability v, exposure x, sleep loss s, and stress q:

$$z = a + b_1 v + b_2 x + b_3 s + b_4 q + b_5 xs + b_6 xv.$$

If a transition becomes more likely when z exceeds a threshold, equal THC exposure will have larger consequences near that threshold. The equation is illustrative. Its coefficients are unknown; the latent variable is not a biomarker. It prevents a common logical error: because most exposed people do not cross a threshold, the exposure cannot contribute to those who do.

Established evidence, synthesis, and hypothesis

Established: THC acts at CB1, acutely impairs cognition, can cause psychotic-like symptoms, and repeated use can produce tolerance, withdrawal, and CUD. Supported by convergence: early frequent high-THC use carries greater CUD and psychosis risk; continued use after psychosis predicts relapse. Flow Hijacked synthesis: these processes interact as a nonlinear landscape of learning and vulnerability. New hypothesis: state-dependent precision weighting and transition dynamics can prospectively predict escalation or adverse reactions. Keeping the levels separate is not rhetorical caution; it is the condition for a useful theory.

24. Myths and half-truths Back to TOC

“Natural means safe”

Natural origin says nothing decisive about dose, receptor action, smoke, contamination, or vulnerability. Many beneficial medicines and potent toxins are natural. Cannabis contains biologically active molecules; that is why it can help and harm. The correction is not “natural means dangerous” but “origin is not a safety evaluation.”

“Cannabis is harmless”

False as a general claim. Acute impairment, panic, CUD, withdrawal, psychosis risk, airway irritation from smoking, CHS, driving impairment, pediatric poisoning, and pregnancy concerns are supported to differing degrees. Harm is not uniform, and many users do not develop severe outcomes. The accurate unit is a product–dose–person–time trajectory.

“Cannabis destroys the brain”

Unsupported as a universal statement. Acute cognitive impairment is well established; frequent youth use is associated with small average cognitive differences; imaging findings are heterogeneous; many measures improve with abstinence. Heavy early exposure may carry persistent risk in some people, and missed learning can endure without a permanent lesion. The evidence supports caution, not a cartoon of neuronal ruin.

“CBD cancels THC”

Not reliably. CBD and THC have different pharmacology, and CBD can alter selected effects in context-dependent ways. Recent controlled studies do not show dependable protection from THC-related cognitive, psychotic, or driving impairment at common ratios. CBD can also raise THC exposure by metabolic interaction under some conditions. Less THC is more reliably less THC.

"Cannabis is not addictive"

False. CUD is a validated disorder; tolerance and withdrawal are real; roughly one-fifth of ever-user samples and larger fractions of current frequent users meet varying disorder definitions. Risk is higher with early regular, daily, and high-THC exposure. Addiction is an adaptive learning and neurobiological process, not weakness.

"Everyone who uses becomes addicted"

False. Most people who ever use do not develop severe CUD. Risk estimates depend on denominator and pattern. Recognizing distribution prevents both stigma and complacency.

"Indica sedates; sativa stimulates"

Commercial labels do not reliably encode chemistry or genetic ancestry. Expectation and aroma can shape experience, and products genuinely differ. THC dose, CBD, other constituents, route, tolerance, and setting are more informative than the binary label.

"Medical use proves recreational safety"

A standardized formulation can be effective for one indication and unsafe in another context. Opioids are medical and risky; chemotherapy is medical and toxic. Pharmaceutical CBD trials do not validate high-THC concentrates or smoke exposure. Evidence attaches to the specific intervention and outcome.

"Cannabis causes schizophrenia"

Too absolute. Cannabis is neither necessary nor sufficient. Schizophrenia has multiple causes. The stronger, narrower statement is that THC probably makes a causal contribution to psychosis in some people, with greater risk under frequent high-potency exposure and vulnerability.

"Cannabis has nothing to do with schizophrenia"

Inconsistent with controlled THC effects, dose-response studies, potency patterns, earlier onset, transition after cannabis-induced psychosis, and relapse with continued use. Confounding and bidirectionality modify causal estimates; they do not erase the convergent signal.

25. Harm reduction without instructions for intoxication Back to TOC

Prevention has a gradient

The largest developmental gain comes from delaying initiation and preventing experimental use from becoming frequent high-THC use. Delay is not based on a magical age; it reduces exposure during ongoing development and shortens cumulative opportunity for dependence. For people who use, reducing frequency and avoiding high-potency THC can reduce several risks. Avoiding smoke reduces combustion-related risk but does not remove intoxication or dependence.

Educational harm reduction does not require teaching how to maximize an effect. It identifies conditions that predict harm:

- do not drive, operate machinery, or combine cannabis with alcohol while impaired;
- keep intoxicating products securely away from children and animals and preserve original labeling;
- treat delayed oral effects as capable of lasting longer than expected rather than assuming no effect;

- avoid THC when pregnant or breastfeeding and seek effective alternatives for the symptom being treated;
- take new paranoia, hallucinations, mania, chest pain, fainting, or persistent vomiting seriously;
- notice escalation, failed efforts to cut down, morning or all-day use, withdrawal, role failure, and narrowing activities;
- ask a pharmacist or clinician about interactions, especially with pharmaceutical-dose CBD, sedatives, antiseizure drugs, anticoagulants, or narrow-therapeutic-index medicines.

These principles do not define a safe dose. They prioritize high-leverage reductions and early recognition.

When help is urgent

Emergency assessment is appropriate for severe confusion, psychosis with unsafe behavior, seizure, loss of consciousness, chest pain, stroke-like symptoms, suicidal intent, or persistent vomiting with dehydration. A calm environment and nonjudgmental communication help, but they do not replace medical care.

When help is not an emergency but matters

Dependence often presents quietly: sleep becomes impossible without use, plans to reduce repeatedly fail, tolerance rises, or relationships and work narrow. Primary care, addiction medicine, psychiatry, youth services, and evidence-based psychotherapy can help. A clinician should ask what use is accomplishing and treat co-occurring pain, trauma, ADHD, mood, or insomnia. Removing the drug without replacing its function is an incomplete plan.

A public-health hierarchy

Population measures can target accurate potency and serving labels, child-resistant packaging, contamination testing, marketing restrictions, surveillance of high-THC products, impaired-driving prevention, nonpunitive pregnancy care, and treatment access. Legalization and prohibition each carry effects beyond pharmacology. A scientific policy evaluation should measure use patterns, CUD, psychosis, poisonings, equity, criminal-justice harms, and commercial exposure rather than using one outcome as the verdict.

26. The frontier: credible questions without premature answers Back to TOC

Circuit-specific cannabinoid signaling

New genetic, optical, and molecular tools can distinguish CB1 effects by cell type, projection, and time. The same receptor on a GABA terminal and glutamate terminal can push a circuit in different directions. Biased signaling and receptor heteromers may offer therapeutic specificity, but translation from engineered systems to humans is early. A “CB1 drug” is not one functional category.

Developmental neuroimaging and intensive measurement

Large prospective cohorts now collect repeated imaging, cognition, genetics, environment, and substance use before and after initiation. Their promise depends on better cannabinoid exposure measurement, preregistration, within-person models, and independent replication. Wearable sleep and ecological momentary assessment can locate exposure within real stress and learning. The field must avoid treating repeated publications from one cohort as repeated cohorts.

Genetics and polygenic vulnerability

Large multi-ancestry genome-wide studies confirm that CUD is polygenic and genetically correlated with other substance-use and psychiatric traits (Levey et al., 2023). This advances biology at the population level. Current polygenic scores lack accuracy, ancestry portability, and clinical specificity for predicting who will develop CUD or psychosis after cannabis. Family and clinical history remain more actionable.

Sex differences

Sex hormones interact with endocannabinoid signaling, and preclinical studies suggest sex-dependent sensitivity, tolerance, stress effects, and developmental consequences. Human findings are mixed and entangled with dose, product, body composition, social exposure, and gendered patterns of use. “Women are more sensitive” or “men are at greater risk” is too coarse. Sex-stratified, adequately powered work is needed.

Epigenetics, immune signaling, and microglia

Cannabis exposure is associated with epigenetic differences in sperm, blood, or other tissues, and adolescent THC changes microglial and synaptic outcomes in animal models. These findings are preclinical or observational, tissue-specific, and vulnerable to tobacco and other confounding. A methylation difference is not evidence of inherited disease; a microglial change in a mouse is not a human cognitive diagnosis (Hasegawa et al., 2023; Holloman et al., 2021).

Computational psychiatry and biomarkers

Computational tasks can estimate learning rate, uncertainty, reward sensitivity, and belief updating. Combined with pharmacological challenge and longitudinal sampling, they might identify mechanisms of paranoia or relapse. Biomarkers must predict outcomes beyond age, frequency, potency, symptoms, and history before adding clinical value. At present there is no blood test, scan, or polygenic score that certifies an individual as safe for high-THC use.

Precision cannabinoid medicine

Precision medicine would match a characterized molecule and formulation to an indication, metabolism profile, co-medications, vulnerability, and meaningful outcome. It requires standardized products, dose–exposure data, interaction studies, long follow-up, validated responder definitions, and transparent harms. Current retail categories are far from this standard. Novel cannabinoid therapeutics may exploit CB2, peripheral CB1, enzyme modulation, allosteric sites, or biased signaling without reproducing THC intoxication. Past failures and toxicities counsel humility.

The research program the field needs

The next generation of studies should measure actual THC and CBD exposure, not only “use”; oversample early frequent and concentrate users; establish baseline cognition and symptoms; distinguish acute, residual, withdrawal, and persistent effects; report absolute as well as relative risk; analyze cessation and reduction; include diverse ancestry and sex; and preregister causal models. Therapeutic trials need active comparators, blinding checks, function, CUD outcomes, and years rather than weeks of follow-up.

27. Conclusion: precision is an ethic Back to TOC

Cannabis is a plant, a changing product market, a set of molecules, a route-dependent pharmacological event, a social practice, a medicine in selected forms, and a possible object of addiction. Collapsing these layers makes both advocacy and warning less truthful.

THC and CBD are pharmacologically different. The endocannabinoid system is a fundamental regulatory architecture, not a wellness slogan. Modern high-THC products can create exposures unlike historical low-potency plant material. CUD is real. Developmental timing matters without a magical age of completion. Psychosis deserves serious attention without claiming that cannabis explains all schizophrenia. Standardized cannabinoids have genuine therapeutic value in selected indications, and that value does not generalize to every product.

The evidence is asymmetric. Acute THC impairment, psychotomimetic effects, tolerance, withdrawal, and pharmaceutical CBD efficacy in named epilepsy syndromes are well established. A causal contribution to psychosis under frequent high-THC exposure is supported by convergence but cannot be assigned with certainty in one individual. Chronic cognitive, mood, cardiovascular, reproductive, and prenatal developmental estimates carry more confounding and heterogeneity. Uncertainty should change verbs, not make the subject disappear.

The Flow Hijacked view adds one disciplined idea: outcomes emerge from trajectories in adaptive systems. Dose meets history. Relief teaches repetition. Withdrawal alters the sober baseline. Stress tilts the landscape. Development changes what is being learned. Environment supplies or removes alternatives. Similar exposures can therefore lead to pleasure, medicine, transient impairment, dependence, or destabilization.

Compassion follows from this model. A person is never reducible to a product choice or diagnosis. The question is not whether they were strong enough to resist a molecule. It is how biology, learning, suffering, pleasure, opportunity, and product design came to organize a path—and which changes can open another one.

Precision is not coldness. It is the refusal to exaggerate a risk, erase a benefit, hide a limitation, or abandon a person inside a slogan.

Appendices Back to TOC

Appendix A — Research acquisition and evidence architecture Back to TOC

Scope and cutoff

The evidence search closed on 4 September 2026. The acquisition process began with broad subject discovery, then moved to structured domain searches, source validation, evidence extraction, contradiction search, and claim-level grading. The scientific corpus contains 202 topic-valid PubMed-indexed records selected from 863 machine-retrieved candidates, plus fourteen authoritative reports, guidelines, regulatory documents, and data sources, for 216 frozen sources. The working evidence ledger contains 116 load-bearing claims.

The corpus is intentionally weighted toward systematic reviews, meta-analyses, umbrella reviews, randomized trials, prospective cohorts, registries, genetically informed designs, experimental pharmacology, neuroimaging, and major clinical guidance. Recency was not allowed to replace design quality. Older work was retained when it established receptor pharmacology, pharmacokinetics, diagnostic validity, or pivotal clinical efficacy.

Discovery reference: the supplied video

The complete Huberman Lab episode *The Effects of Cannabis (Marijuana) on the Brain & Body* was used as a conceptual and subject-discovery reference. Its structure helped identify questions about product categories, routes, the endocannabinoid system, hormones, cognition, psychosis, creativity, and developmental timing. It was not entered as scientific evidence and is not used to support a substantive claim. Every scientific claim drawn from its topic map was independently checked.

Acquisition domains

Queries were organized across thirteen intersecting domains: plant biology and chemistry; product taxonomy and potency; endocannabinoid molecular neuroscience; THC/CBD pharmacology; pharmacokinetics and route; acute cognition; adolescent development and neuroimaging; psychosis and causal inference; mood and self-medication; CUD and withdrawal; physical health and driving; pregnancy and reproduction; therapeutics, interactions, and frontier science.

Searches used controlled and free-text combinations for cannabis, marijuana, cannabinoid, THC, cannabidiol, CB1, CB2, anandamide, 2-AG, psychosis, cognition, adolescent, pregnancy, driving, potency, concentrate, withdrawal, and indication-specific terms. Retrieval favored human evidence while preserving mechanistically necessary preclinical work. Authoritative materials were obtained from NASEM, AHRQ, FDA, ACOG, NICE, WHO, EUDA, NIDA, and transport-safety authorities.

Inclusion hierarchy

At the top of the hierarchy were current high-quality systematic syntheses and authoritative guidelines with transparent methods. For treatment efficacy, randomized trials and regulatory review dominated. For rare harms and long latency, large cohorts, registries, and case-control studies were necessary. Genetically informed studies were used to interrogate shared liability, not treated as automatic causal verdicts. Experimental THC challenge linked receptor-active exposure to acute cognition and psychotic-like symptoms. Animal and cellular studies were confined to mechanism and explicitly labeled preclinical.

Sources were down-weighted for undefined exposure, conflation of lifetime and daily use, absent potency, cross-sectional design, weak control of tobacco or premorbid symptoms, small imaging samples, uncorrected multiplicity, outcome switching, industry-linked interpretation without adequate disclosure, and extrapolation from animals to clinical outcomes. A large sample did not compensate for a badly measured exposure.

The causal ladder

The manuscript uses the following ladder:

1. **Presence or co-occurrence:** a compound, receptor, diagnosis, or population association is observed.
2. **Longitudinal prediction:** exposure precedes outcome, with remaining concern about shared causes.
3. **Dose-response:** risk changes with frequency, dose, or potency, strengthening but not proving causality.
4. **Mechanistic plausibility:** receptor, circuit, or learning evidence supplies a credible route.
5. **Experimental causality:** randomized exposure changes an acute outcome.
6. **Triangulated causal contribution:** several designs with different biases converge.
7. **Established clinical causality:** replicated trials or highly specific evidence supports a defined intervention–outcome pair.

The ladder is outcome-specific. THC experimentally causes acute impairment; randomized trials cannot ethically establish decades-later schizophrenia. Pharmaceutical CBD efficacy in named epilepsy syndromes is established; a CB2 effect in a mouse does not establish human anti-inflammatory treatment.

Evidence ledger fields

Each major claim was recorded with domain, claim category, exact wording, permitted evidence language, source, study design, sample and population, exposure, potency where available, age, outcome, effect estimate, confounders, disconfirming evidence, limitations, and confidence. Claims were revised downward when the evidence could not support the initial verb. The complete ledger accompanies this monograph as a machine-readable table.

Adversarial audits

Before drafting, the corpus was challenged for causal overreach, binary exposure, relative-risk inflation, psychosis simplification, commercial chemistry claims, and therapeutic transfer. A separate under-25 audit prohibited the “brain finishes at 25” claim, required separation of single from repeated exposure, and forced imaging findings to be described as associations unless stronger designs justified more. After drafting, every numerical claim was checked against its ledger row, all age-related statements were reviewed again, and Flow Hijacked language was tagged as synthesis or hypothesis rather than discovered mechanism.

Appendix B — Evidence-at-a-glance tables Back to TOC

B1. Harms, development, and addiction

Question	Best current answer	Evidence form	Important estimate	Confidence and boundary
Does acute THC impair cognition?	Yes; learning, working memory, divided attention, psychomotor function	Controlled trials and systematic reviews	Effect varies by task and dose	Strong; tolerance can mask subjective effect

Question	Best current answer	Evidence form	Important estimate	Confidence and boundary
Does youth heavy use associate with cognitive difference?	Yes, small on average	69-study meta-analysis	SMD about −0.25	Moderate; mostly cross-sectional and heterogeneous
Do deficits shrink with abstinence?	Often	Meta-analytic moderator and monitored studies	>72 h subgroup about −0.08, not significant	Moderate; not proof of universal full recovery
Does development stop at 25?	No	Lifespan neuroscience	No universal endpoint	Strong
Does early regular use predict CUD?	Yes	Cohorts and meta-analysis	Young regular-use dependence estimates around one-third in some cohorts	Moderate–strong; shared liability matters
Can cannabis be addictive?	Yes	Diagnostic, epidemiological, withdrawal, treatment evidence	CUD about 22% across ever-user studies; higher in current users	Strong for disorder; percentage depends on denominator
Is withdrawal real?	Yes	47-study meta-analysis and clinical review	Pooled prevalence about 47% in regular/dependent samples	Strong; setting heterogeneity large
Does high potency matter?	Most clearly for psychosis and CUD	Systematic reviews, case-control, pharmacology	No universal potency threshold	Moderate; product-level measurement remains limited
Does cannabis cause psychotic-like symptoms acutely?	THC can	Placebo-controlled challenge meta-analysis	15 studies, 331 participants; large symptom increases	Strong; acute symptoms are not schizophrenia
Is cannabis related to psychotic disorder?	Probable causal contribution in some people	Experimental, dose-response, longitudinal, genetic, cessation evidence	Heaviest-use OR 3.90; EU-GEI daily high-potency OR 4.8	Moderate–strong; not necessary or sufficient
What follows cannabis-induced psychosis?	Substantial transition risk	Registry and meta-analysis	About 34% in 2020 synthesis; newer estimates vary	Strong for high risk, moderate for exact fraction
Does stopping after psychosis matter?	Better trajectories associate with cessation	Prospective cohorts	Lower relapse/hospitalization than continued use	Moderate–strong; not fully randomized
Does cannabis cause depression?	Association is modest; causality uncertain	Longitudinal meta-analysis	Adolescent use → depression OR 1.37	Moderate for association
Does it cause suicide?	Associated with ideation/attempt; no simple direct path established	Reviews and cohorts	Youth exposure meta-analysis: ideation OR 1.50, attempt OR 3.46	Moderate association; limited causal specificity
Does it worsen bipolar illness?	Associated with mania and worse course	Meta-analyses	Some pooled effects around two- to threefold	Moderate association; bidirectionality probable

B2. Physical health and safety

Question	Best current answer	Evidence form	Important estimate	Confidence and boundary
Does smoking irritate airways?	Yes	Systematic review	More cough, sputum, wheeze	Moderate–strong
Does cannabis alone cause COPD or lung cancer?	Uncertain	Cohorts and reviews	Results inconsistent	Moderate confidence in uncertainty; exposure poorly measured
Does THC affect the cardiovascular system?	Acutely raises heart rate and alters blood pressure	Experimental physiology	Event-risk magnitude uncertain	Strong physiology, moderate event association
Are cardiovascular events associated?	Yes in recent observational synthesis	24-study meta-analysis	RR 1.29 ACS; 1.20 stroke; 2.10 CV mortality	Moderate; residual confounding and earlier null synthesis
Is CHS real?	Yes, after prolonged frequent exposure	Clinical patterns and reviews	Incidence unknown	Strong for syndrome; cessation most reliable prevention
Does prenatal exposure matter?	Associated with adverse birth outcomes	~51 studies, >21 million pregnancies	OR 1.75 low birth weight; 1.52 preterm; 1.57 SGA	Moderate–strong association; residual confounding

Question	Best current answer	Evidence form	Important estimate	Confidence and boundary
Is long-term child neurodevelopment affected?	Attention/behavior signals; global results mixed	Observational reviews	No single dependable absolute effect	Moderate association, limited causal precision
Does cannabis impair driving?	Yes acutely	Experimental and crash syntheses	Older crash OR about 1.92, heterogeneous	Strong impairment; moderate exact crash effect
Can blood THC define impairment?	Not with one reliable universal threshold	Systematic review	Most studies lack linear performance relation	Strong limitation
Does alcohol add risk?	Yes	Controlled driving studies	Greater impairment than either alone	Strong
Are SCRAs just stronger THC?	No	Receptor pharmacology and toxicology	Full/high-efficacy agonism common	Strong distinction

B3. Therapeutic evidence

Indication	Product or class	Grade	What benefit is supported?	Principal harms or limits
Dravet, Lennox–Gastaut, tuberous sclerosis seizures	Purified pharmaceutical CBD	Strong/established	Reduced seizure frequency as add-on	Somnolence, diarrhea, appetite, liver enzymes; interactions
Chemotherapy nausea/vomiting	Dronabinol, nabilone, standardized THC/CBD	Moderate	Benefit in selected refractory/adjunctive use	Psychoactive effects; older evidence predates modern antiemetics
MS spasticity	Nabiximols/standardized products	Moderate	Modest short-term patient-reported improvement	Objective measures less consistent; dizziness/psychiatric effects
Chronic/neuropathic pain	Some THC-containing or balanced products	Moderate, modest	Small short-term pain reduction	Limited function; sedation, dizziness, nausea; short trials
Palliative symptoms broadly	Mixed cannabinoids	Limited/inconclusive	No dependable broad quality-of-life effect	Heterogeneous diseases/products; attrition
Primary insomnia	THC/CBD products	Limited	Sparse signals; more evidence in pain-related sleep	Tolerance, architecture change, rebound insomnia
Anxiety disorders	CBD/cannabinoids	Limited/conflicting	Small studies positive; no reliable pooled disorder benefit	Dose mismatch, short follow-up, THC anxiety
PTSD	Mixed	Inconclusive to negative	Overall symptoms not reliably improved in controlled synthesis	Self-selection; sleep-only signals; CUD risk
Psychosis	High-dose purified CBD adjunct	Limited/conflicting	One positive trial; pooled benefit unclear	Not equivalent to consumer CBD; drug interactions
Depression	Cannabinoids	Inadequately studied	No qualifying efficacy base in recent RCT synthesis	THC may worsen some trajectories

Appendix C — Supplied-video discovery and correction map Back to TOC

The supplied episode was useful because it tried to connect molecular pharmacology with lived effects. Its strongest structural contributions were to ask what cannabis products contain, why route matters, how CB1-rich circuits relate to memory and movement, why THC and CBD differ, and why adolescence, psychosis, hormones, and creativity require separate treatment. Those questions are preserved here.

Several explanations required correction or narrowing. Commercial *sativa* and *indica* labels were too readily mapped onto stimulant and sedative effects; chemical and genetic surveys do not support that precision. CBD should not be described as a potent CB1 agonist. CBN is cannabinol, not cannabidiol. Oral, inhaled, and sublingual time courses require more uncertainty than fixed onset claims. Detection of THC or metabolites is not a measure of current impairment. Claims about prolactin, testosterone, fertility, and cortical thinning were too broad for the human evidence. The idea that the brain completes development at exactly twenty-five was replaced with continuous heterogeneous trajectories. Depression associations were separated from causal proof. Smoking and vaping were separated rather than treated as the same pulmonary exposure. Potency was treated as a dose-enabling variable with uneven outcome-specific evidence.

The episode's role ended at question discovery. No conclusion in this monograph depends on its authority.

Appendix D — Glossary Back to TOC

11-hydroxy-THC (11-OH-THC): Psychoactive THC metabolite formed in the liver, proportionally prominent after oral exposure.

Absolute risk: Probability of an outcome in a defined population and time period; necessary for interpreting relative effects.

Agonist: Ligand that activates a receptor. Efficacy can be partial or full and depends on the assay and system.

Allosteric modulator: Compound binding outside a receptor's primary ligand site and changing the receptor's response.

Anandamide (AEA): Endogenous cannabinoid lipid, also called *N*-arachidonoylethanolamine; degraded largely by FAAH.

Association: Statistical relationship that may reflect causation, reverse causation, confounding, or combinations.

Attractor: In a dynamical model, a state or set toward which trajectories tend to evolve.

Bioavailability: Fraction of an administered dose reaching systemic circulation in usable form.

Biased signaling: Preferential activation of some downstream receptor pathways over others by different ligands.

Cannabinoid: Broad term for plant-derived, endogenous, or synthetic molecules that engage cannabinoid-related biology.

Cannabis-induced psychotic disorder: Prominent delusions or hallucinations temporally related to cannabis and exceeding ordinary intoxication; requires clinical assessment.

Cannabis Use Disorder: Diagnostic syndrome of impaired control, salience, risky or continued use, role effects, tolerance, or withdrawal, graded by criterion count.

CB1: Cannabinoid type-1 receptor, abundant at presynaptic terminals throughout the brain and present peripherally.

CB2: Cannabinoid type-2 receptor, prominent in immune biology and present in nervous-system cells under context-dependent conditions.

CBD (cannabidiol): Non-intoxicating phytocannabinoid with low CB1/CB2 orthosteric affinity and multiple proposed targets; an approved medicine in specific epilepsy syndromes.

CBDA: Cannabidiolic acid, a plant precursor that can decarboxylate to CBD.

CBG: Cannabigerol, a minor neutral phytocannabinoid derived from the CBGA pathway.

CBGA: Cannabigerolic acid, an important biosynthetic precursor to several acidic cannabinoids.

CBN (cannabinol): Cannabinoid associated partly with THC oxidation and degradation; not cannabidiol.

Chemovar: Variety described by measured chemical composition rather than only commercial name or morphology.

Confidence interval: Range produced by a statistical procedure that reflects sampling uncertainty under model assumptions; not the probability that one fixed parameter lies in the observed interval.

Confounder: Factor associated with both exposure and outcome that can distort their estimated relationship.

Counterfactual: Outcome that would have occurred under an alternative exposure or intervention; causal questions compare counterfactual states.

Decarboxylation: Loss of carbon dioxide from acidic cannabinoids, such as THCA becoming THC, promoted by heat and time.

Dependence: Adapted state in which stopping produces withdrawal; related to but not identical with addiction.

Dose-response: Change in outcome as dose, frequency, or potency changes; strengthens causal inference but can still be confounded.

Endocannabinoid: Cannabinoid-like signaling molecule made by the body, especially anandamide and 2-AG.

Entourage effect: Broad label for proposed interactions among cannabis constituents; specific interactions exist, while a general clinically predictable synergy is unestablished.

Exposure vector: Multidimensional description including constituents, dose, route, rate, frequency, duration, developmental timing, co-exposures, and context.

FAAH: Fatty-acid amide hydrolase, a major enzyme degrading anandamide.

First-pass metabolism: Metabolism in gut and liver before an orally administered compound reaches systemic circulation.

Flavonoid: Polyphenolic plant compound; human cannabis-specific pharmacology is largely uncertain.

Full agonist: Ligand capable of producing the system's maximal receptor response under defined assay conditions.

GABA: Gamma-aminobutyric acid, the principal inhibitory neurotransmitter in the mature brain.

Glutamate: Principal excitatory neurotransmitter in the brain.

Homeostasis: Dynamic regulation around functional ranges; does not imply that every external perturbation is corrective.

Longitudinal study: Study that follows participants across time, improving temporal inference but not eliminating confounding.

MAGL: Monoacylglycerol lipase, responsible for much 2-AG hydrolysis in the brain.

Mendelian randomization: Causal-inference design using genetic variants as instruments; vulnerable to pleiotropy, weak instruments, and phenotype mismatch.

Metastability: Temporary stability of coordinated states with capacity to transition, used in complex-systems neuroscience.

Negative reinforcement: Increased behavior because it removes or reduces an aversive state.

Odds ratio: Ratio of odds between groups; can diverge substantially from a risk ratio when outcomes are common.

Partial agonist: Ligand producing less than the maximal response in a defined system even at high receptor occupancy; not synonymous with clinically weak.

Pharmacodynamics: Effects of a drug on the organism and relationship between exposure and response.

Pharmacokinetics: Absorption, distribution, metabolism, and elimination of a drug.

Polygenic risk score: Weighted summary of many genetic variants associated with a trait; currently insufficient for individual cannabis-risk prediction.

Potency: Concentration or strength per unit product; not identical with administered or absorbed dose.

Prediction error: Difference between expected and observed outcome used in learning models.

Predictive processing: Family of theories treating perception and action as inference under uncertainty; application to cannabis is a developing synthesis.

Preclinical: Evidence from cells, tissues, or nonhuman animals, useful for mechanism but not direct proof of human clinical effect.

Prospective cohort: Group assessed before outcomes occur and followed forward, reducing recall problems while retaining selection and confounding.

Psychosis: Syndrome involving impaired reality testing, such as hallucinations, delusions, or disorganization; not one diagnosis.

Psychotomimetic: Producing temporary phenomena resembling aspects of psychosis.

Receptor occupancy: Fraction of available receptors bound by ligand; effect also depends on efficacy, coupling, reserve, and network location.

Relative risk: Ratio of outcome probabilities between groups; must be paired with baseline or absolute risk for personal meaning.

Residual effect: Effect persisting after obvious intoxication but before a sufficiently long verified abstinence interval.

Retrograde signaling: Postsynaptic signal traveling backward to regulate a presynaptic terminal.

Salience: Motivational or attentional importance assigned to a stimulus, thought, or bodily signal.

SCRA: Synthetic cannabinoid receptor agonist; heterogeneous class often with higher CB1 efficacy and toxicity than THC.

Sensitivity analysis: Test of how an estimate changes under alternative assumptions, definitions, or adjustments.

State space: Mathematical representation of possible system states using selected variables.

THC (Δ9-tetrahydrocannabinol): Principal intoxicating phytocannabinoid and partial CB1/CB2 agonist.

THCA: Tetrahydrocannabinolic acid, plant precursor that decarboxylates to THC and is far less intoxicating at typical exposure.

Tolerance: Reduced response after repeated exposure or need for more exposure to obtain a prior effect.

Withdrawal: Reproducible symptoms after reducing or stopping an exposure to which the system has adapted.

2-AG: 2-arachidonoylglycerol, abundant endocannabinoid and agonist at CB1/CB2, degraded largely by MAGL.

Appendix E — Acronym guide Back to TOC

Acronym	Meaning
2-AG	2-arachidonoylglycerol
11-OH-THC	11-hydroxy-THC
ABHD	α/β-hydrolase domain-containing enzyme
ACOG	American College of Obstetricians and Gynecologists
AEA	Anandamide / *N*-arachidonoylethanolamine
AHRQ	Agency for Healthcare Research and Quality
CB1 / CB2	Cannabinoid receptor type 1 / type 2
CBD / CBDA	Cannabidiol / cannabidiolic acid
CBG / CBGA	Cannabigerol / cannabigerolic acid
CBN	Cannabinol
CHS	Cannabinoid hyperemesis syndrome
CI	Confidence interval
CINV	Chemotherapy-induced nausea and vomiting
CUD	Cannabis Use Disorder
CYP	Cytochrome P450 enzyme family
DAGL	Diacylglycerol lipase
DSM-5-TR	*Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, text revision
ECS	Endocannabinoid system
EU-GEI	European Network of National Schizophrenia Networks Studying Gene–Environment Interactions
FAAH	Fatty-acid amide hydrolase
FDA	US Food and Drug Administration

Acronym	Meaning
GABA	Gamma-aminobutyric acid
GWAS	Genome-wide association study
MAGL	Monoacylglycerol lipase
MRI / fMRI	Magnetic resonance imaging / functional MRI
MS	Multiple sclerosis
NASEM	National Academies of Sciences, Engineering, and Medicine
NIDA	National Institute on Drug Abuse
NICE	National Institute for Health and Care Excellence
OR / RR	Odds ratio / risk ratio
PAF	Population-attributable fraction
PET	Positron-emission tomography
PK / PD	Pharmacokinetics / pharmacodynamics
PPAR	Peroxisome proliferator-activated receptor
PRS	Polygenic risk score
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trial
REM	Rapid eye movement sleep
SCRA	Synthetic cannabinoid receptor agonist
SGA	Small for gestational age
SMD	Standardized mean difference
THC / THCA	Δ9-tetrahydrocannabinol / tetrahydrocannabinolic acid
THC-COOH	11-nor-9-carboxy-THC
TRP / TRPV1	Transient receptor potential / vanilloid type 1 channel
VTA	Ventral tegmental area
WHO	World Health Organization

Appendix F — How to read a cannabis claim Back to TOC

Before accepting a headline, ask: Was the exposure ever use, current use, daily use, diagnosed CUD, or measured THC? Was potency known? Did exposure precede outcome? Was the comparison group truly comparable? Were tobacco, alcohol, adversity, prior symptoms, and family liability measured before use? Is the number an odds ratio, risk ratio, absolute difference, or model-based PAF? Does a mechanistic study use a human-relevant compound and concentration? Is a therapeutic product standardized and matched to the advertised product? Was the study long enough to detect tolerance, withdrawal, or functional harm?

Bayesian reasoning makes one further point. Posterior odds equal prior odds multiplied by a likelihood ratio:

$$\text{Posterior odds} = \text{Prior odds} \times \text{Likelihood ratio}.$$

A risk factor can meaningfully update probability without determining outcome. In a low-baseline-risk person, even a strong relative association may leave the absolute probability low; in a high-liability person, the same update can be clinically large. No current cannabis biomarker supplies a precise individual likelihood ratio. The equation disciplines communication; it does not create certainty.

The highest-quality answer is often conditional: *for this product*, *route*, *dose*, *frequency*, *age*, *vulnerability*, *and outcome*, *this design supports this level of confidence*. That sentence is longer than a slogan because the biology is longer than a slogan.

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