74 CANNABINOIDS

Jeff M. Lapoint

HISTORY AND EPIDEMIOLOGY

Cannabis has been used for more than 4,000 years. The earliest documentation of the therapeutic use of marijuana is the fourth century B.C. in China.[172] Cannabis use spread from China to India to North Africa, reaching Europe around A.D. 500.[138] In colonial North America, cannabis was cultivated as a source of fiber. Similar to cocaine and morphine, cannabis was the focus of research efforts in the 19th century. Although the active chemical constituents of the former were isolated during this time, that of cannabis remained elusive.[97] This was because the active compounds of opium poppy and coca leaf are both alkaloids and were possible to extract with the technological means of the time, whereas the methods to isolate the active terpenes in cannabis were not available to researchers until several decades later.

The first pure phytocannabinoid to be isolated was cannabinol, in 1898. Synthesis of its structural isomers yielded the first synthetic cannabinoid (SC) years later—Δ^9-tetrahydrocannabinol (THC). Cannabinol was previously shown to lack psychoactive effects, but this new compound demonstrated similar effects to cannabis in a model of ataxia in dogs. Pure Δ^9-THC was subsequently isolated from hashish extract in 1964, and the structure was elucidated in 1967.[98]

Cannabis was used in the United States as a substance of abuse from the 1850s until the 1930s when the US Federal Bureau of Narcotics began to portray marijuana as a powerful, addictive substance. Despite this, marijuana was listed in the US Pharmacopoeia from 1850 to 1942. In 1970, the Controlled Substances Act classified marijuana as a Schedule I drug.

In all populations, cannabis use by men exceeds use by women. Currently, marijuana is the most commonly used illicit xenobiotic in the United States; however, it is legal for recreational use in an increasing number of states, including at the time of this writing Colorado, Washington, California, Oregon, and Alaska. In 2015 in the United States, 8.2% (22 million persons) 12 years of age or older used marijuana in the month before the survey; this prevalence is increased from 6% in previous years. The prevalence of past-month users aged 12 to 17 years was 7% (increased from 6.8% in 2006). The number of first-time users was estimated to be 2.1 million, with 63.3% younger than 18 years of age.[128]

Interest in SCs as potential therapeutics increased after the progress of the late 1960s, and several SCs similar in structure to THC were created. These semisynthetic compounds were based on the dibenzopyran ring structure of THC and had varying cannabinoid receptor binding affinities relative to THC. The search for a nonopioid analgesic sparked research and development efforts by pharmaceutical companies, most notably Pfizer, from the 1960s to 1980s.[67] Despite its efforts, no medications came to market; new analgesics retained unwanted psychoactive side effects. During this period, an extensive understanding of structure activity relationships for cannabinoids developed.[66]

Subsequent synthetic compounds were developed as cannabinoid research tools and were important in the discovery of central and peripheral cannabinoid receptors (CB_1 and CB_2) in the 1980s.[34] Many of these did not retain structural similarity to THC but remained potent and efficacious agonists at CB_1 and CB_2.[66] In the 1990s, the endogenous cannabinoids were discovered and were subsequently synthesized.[84] These free fatty acids are quickly hydrolyzed in vivo, a fact that previously limited potential for pharmaceutical development. Researchers have since synthesized stable versions of endocannabinoids (Fig. 74–1).

In 2004, SC-laced herbal incense blends became available over the Internet and through smoke shops in Western Europe.[88] Popular use and subsequent publicity increased, resulting in several users presenting to emergency departments in Germany. As the result of efforts by the German government and THC Pharma, JWH-018 was isolated as the psychoactive ingredient present in these early incense blends. The discovery led to legislative action and subsequent ban of herbal incense containing JWH-018 in Germany, but almost as soon as the ban took effect, manufacturers substituted a different SC—JWH-073. Since that time, many Western European countries have legislated further control of SCs.

The incidence of SC exposure in the United States increased, and in November 2010, the Drug Enforcement Administration (DEA) began the process of listing selected SCs as Schedule I drugs on a temporary basis. By March 2011, the DEA listed several nonclassical SCs as Schedule I, but as was the case in Germany, manufacturers of herbal incense blends in the United States switched to other unscheduled SCs. Second- and third-generation SCs, such as AM-2201, XLR-11, and the indazole derivatives, have since emerged and further complicate the clinical, regulatory, and public health efforts.

Toxicologists face a new era in the field of cannabinoids: Research continues to advance understanding of the cannabinoid system, a myriad of new and discrete SCs emerge ever year, and even the familiar marijuana is found with higher potency and changing phytocannabinoid ratios that may affect patients in unanticipated ways.

MEDICAL USES

Cannabis has been used medicinally for thousands of years to treat a seemingly endless array of conditions. However, modern medicine is supported by an evidence-based system rather than the belief-based medicine of the past. Therefore, potential medicinals must be proven through rigorous investigation to be not only safe but effective in the treatment of a targeted malady. Although smoked marijuana and THC preparations have not typically proven acutely dangerous, efficacy is questionable. Several issues must be considered when examining the body of evidence both for and against the medical use of cannabinoids. Marijuana is not the same entity as, nor is interchangeable with, Δ^9-THC. Although the latter is the chief psychoactive constituent of marijuana, the multiple additional cannabinoids present in marijuana are biologically active and must be considered. Second, significant study design flaws limit the conclusions that can be drawn from existing studies. Finally, poor overall understanding of cannabinoid physiology may hamper future study design. Proposed uses for medical cannabis and the available evidence supporting that use are reviewed next.

Pain

Acute Pain

Studies examining the efficacy of cannabis in the setting of induced acute pain showed no improvement. These studies were limited by the lack of a positive control and examined only extremes of induced pain.[30] Smoked marijuana failed to attenuate thermal pain in volunteers, and an oral THC analog had no effect on postsurgical pain.[73]

Chronic Pain

When used for the treatment of chronic and neuropathic pain, cannabinoids have had some favorable outcomes, although design flaws severely limit the quality of medical evidence.[118] Initial trials of combined cannabinoid and opioid therapy are encouraging, and the principle may have mechanistic merit based on the knowledge that opioid and cannabinoid receptors can form heterodimers,[131] but lack of proper controls and the presence of confounders limit the clinical applicability of cannabinoids as analgesics at this time.

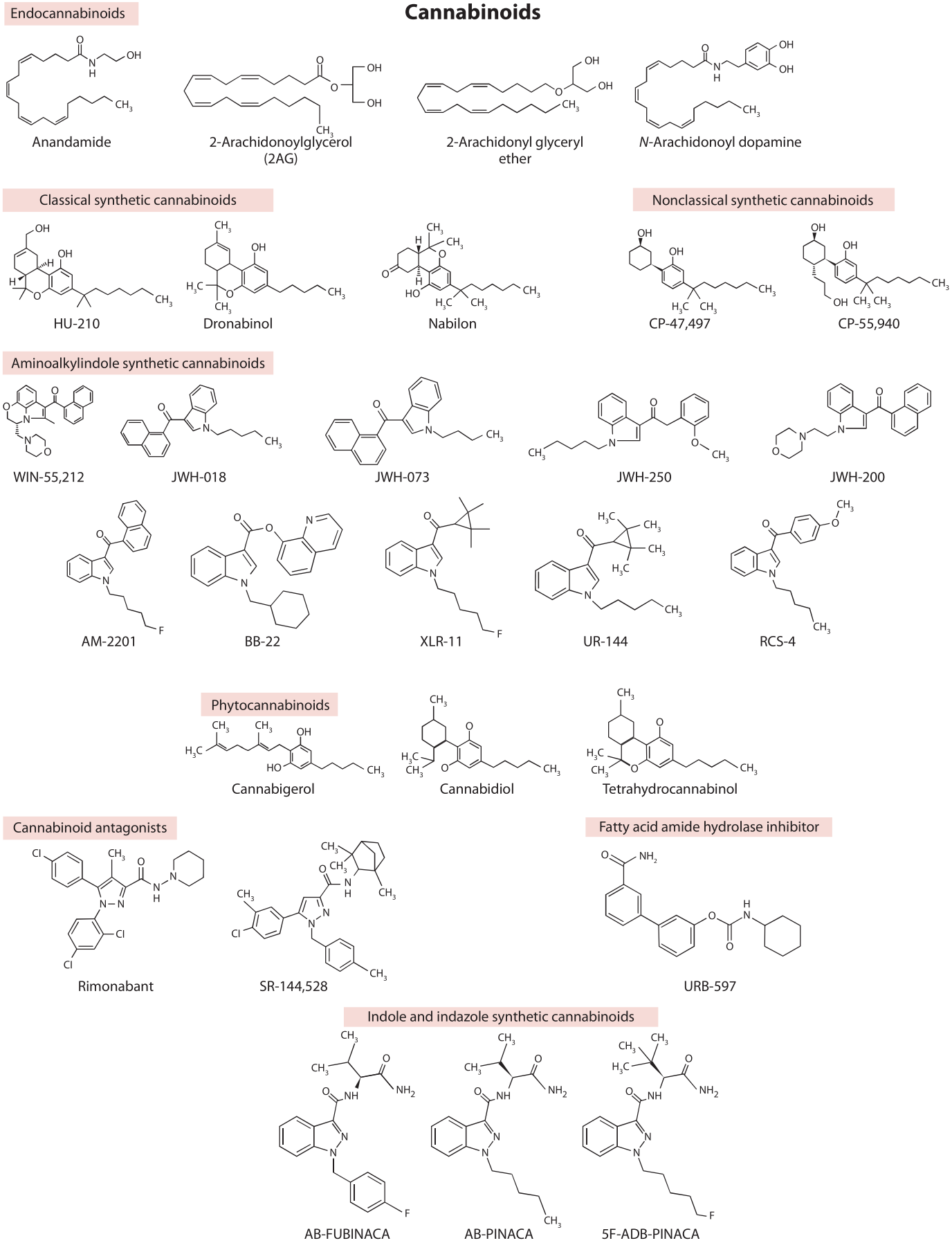

FIGURE 74–1. Cannabinoid structural classes.

Nausea and Vomiting

Trials of cannabinoids for treatment of chemotherapy-induced nausea and vomiting demonstrate superiority over placebo but compared with serotonin and dopamine antagonists, this difference is not statistically significant.[17,38,90,100,169] Dronabinol is currently FDA approved for this indication.

Glaucoma

Trials investigating the efficacy of cannabinoids for the treatment of glaucoma demonstrate the inferiority to longer acting traditional therapeutics, which have more significant effects on intraocular pressure (IOP) and longer durations of effect. One small trial found no difference between the effect of cannabinoids and placebo on IOP.[162]

Summary of Medical Use

In 2003, the Institute of Medicine undertook an extensive review of the evidence supporting the medical use of marijuana. It concluded that in some circumstances, cannabinoids show promise for use as therapeutics, but the quality of current studies necessitated further research specifically for the treatment of chronic pain. In addition, smoking marijuana provides a crude and unpredictable delivery mechanism, and safer, more precise methods of administration are needed.[167]

Similarly, a meta-analysis in 2015 composed of randomized clinical trials (RCTs) showed only moderate evidence to support the efficacy of cannabinoids in treating chronic pain and spasticity related to multiple sclerosis.[169] A Cochrane review of 23 RCTs found that pharmaceutical cannabinoids for use in the management of many clinical conditions but are only currently FDA approved for the control of chemotherapy-related nausea and vomiting that are resistant to conventional antiemetics, for breakthrough postoperative nausea and vomiting, and for appetite stimulation in patients with human immunodeficiency virus (HIV) patients with anorexia-cachexia syndrome.[59] The claims of benefit in the other medical conditions are not clearly supported by evidence.[6,170]

PHARMACOLOGY AND PATHOPHYSIOLOGY

The term *cannabinoid* refers to compounds that bind to the cannabinoid receptors regardless of whether they are derived from plants (phytocannabinoids), synthetic processes (SCs), or endogenous sources (endocannabinoids). At one time, the term may have been used to delineate a structural similarity to Δ^9-THC, but this naming convention was largely abandoned during the past 30 years of cannabinoid research as new compounds were discovered and synthesized. The structural diversity of cannabinoid receptor ligands and the absence of a true pharmacophore make nomenclature based purely on structure cumbersome and inconsistent. It is preferable then to use the term *cannabinoid* to denote receptor binding and subclassify cannabinoids further based on origin and structure (Fig. 74–1). The *terms cannabinoid, cannabinometic,* and *cannabinoid receptor agonist* are interchangeable.

Cannabis is a collective term referring to the bioactive substances from the cannabis plant. The *Cannabis* genus (species *sativa* and *indica*) produces more than 60 chemicals (C21 group) called cannabinoids. The major cannabinoids are cannabinol, cannabidiol (CBD), and tetrahydrocannabinol. The principal psychoactive cannabinoid is THC, also known as Δ^9-tetrahydrocannabinol. *Marijuana* is the common name for a mixture of dried leaves and flowers of the *C. sativa* plant. Hashish and hashish oil are the pressed resin and the oil expressed from the pressed resin, respectively. The concentration of THC varies from 1% in low-potency marijuana up to 50% in hash oil. Δ^9-Tetrahydrocannabinol extracted from marijuana using butane (butane hash oil or BHO) approaches THC concentrations of 100%. Pure THC and several pharmaceutical SCs are available by prescription with the generic names of dronabinol and nabilone, respectively. Nabiximol is the generic name for an oral mucosal spray containing THC and cannabidiol, which is approved for medical use in Canada, the United Kingdom, and parts of Europe. Unregulated SCs originally designed as research chemicals have emerged as designer drugs of abuse over the past several years.

Cannabinoid receptors are G protein–linked neuromodulators that inhibit adenyl cyclase in a dose-dependent and stereospecific manner. Although historically the cannabinoid receptor system is described as having a central CB_1 and a peripheral CB_2 receptor, the available evidence points to the central nervous system (CNS) presence of CB_2 receptors.[147] The two currently identified cannabinoid receptors are labeled CB_1 and CB_2 and are distinguished largely by their anatomic distribution and mechanisms of cellular messaging (Fig. 74–2).

CB_1 Receptors and the Psychogenic Effects of Cannabis

The CB_1 receptors are structurally composed of seven transmembrane protein units coupled to pertussis-sensitive (decrease adenyl cyclase) G proteins. They exhibit genetic variation via splice variants and are found as heterodimers with a multitude of other receptor types.[67]

Isolated agonism of CB_2 receptors was the target for novel pharmaceutical candidates as antiinflammatory agents with minimal success as the psychoactive effects of CB_1 agonism persisted.

The CB_1 receptors are the most numerous G protein–coupled receptors in the mammalian brain, accounting for the multiple and varied effects of cannabinoids on behavior, learning, and mood as well as suggesting the enormous complexity of the endocannabinoid system.[58] The highest concentration of CB_1 receptors is located in areas of the brain associated with movement and higher functions of cognition and emotions. A relative lack of CB_1 receptors in the brainstem also explains lack of coma and respiratory depression that occurs with *Cannabis* use.

Mechanism of Cellular Signaling

Cannabinoid receptors both in the CNS and in the periphery exist on the presynaptic terminus of various neurons. Depolarization in the postsynaptic portion of the neuron and subsequent increase in intracellular Ca^{2+} leads to on-demand synthesis and release of endocannabioids.[117] These free fatty acid–based messengers diffuse into the synapse and bind to the presynaptic cannabinoid receptor. Ligand binding causes conformational change in the G protein subunits and inhibition of adenyl cyclase, resulting in decreased intracellular cyclic adenosine monophosphate (cAMP) concentrations, decreased activity of voltage-gated Ca^{2+} channels, and ultimately decreased neurotransmitter release (Fig. 74–2). Exogenous cannabinoids act similarly to endogenous cannabinoids upon receptor binding, except that binding affinity will vary among exogenous ligands and endogenous cannabinoids, which are rapidly metabolized by fatty acid amide hydrolases.[84] Interestingly, some online chemical suppliers offer fatty acid amide hydrolase inhibitors for sale, along with various SCs, perhaps providing a glimpse into future products more closely related to endocannabinoids coming to market.

Both receptors inhibit adenyl cyclase and stimulate K^+ channel conductance.[121] CB_1 receptors are located either presynaptically or postsynaptically, and their activation can inhibit or enhance the release of acetylcholine, L-glutamate, γ-aminobutyric acid, noradrenaline, dopamine, and 5-hydroxytryptamine.[71,77,140]

The neuropharmacologic mechanisms by which cannabinoids produce their psychoactive effects are not fully elucidated.[60,71,121] Nevertheless, activity at the CB_1 receptors is believed to be responsible for the clinical effects of cannabinoids,[12,40,71,153] including the regulation of cognition, memory, motor activities, nociception, nausea, and vomiting. Chronic administration of a cannabinoid agonist reduces CB_1 receptor density in several regions of the rat brain.[13]

PHARMACOKINETICS AND TOXICOKINETICS

Absorption

The pharmacokinetics of phytocannabinoids was extensively reviewed.[50] The rate and completeness of absorption of cannabinoids depend on the route of administration and the type of cannabis product.

Inhalation of smoke containing THC results in the onset of psychoactive effects within minutes typically reaching peak serum concentration before

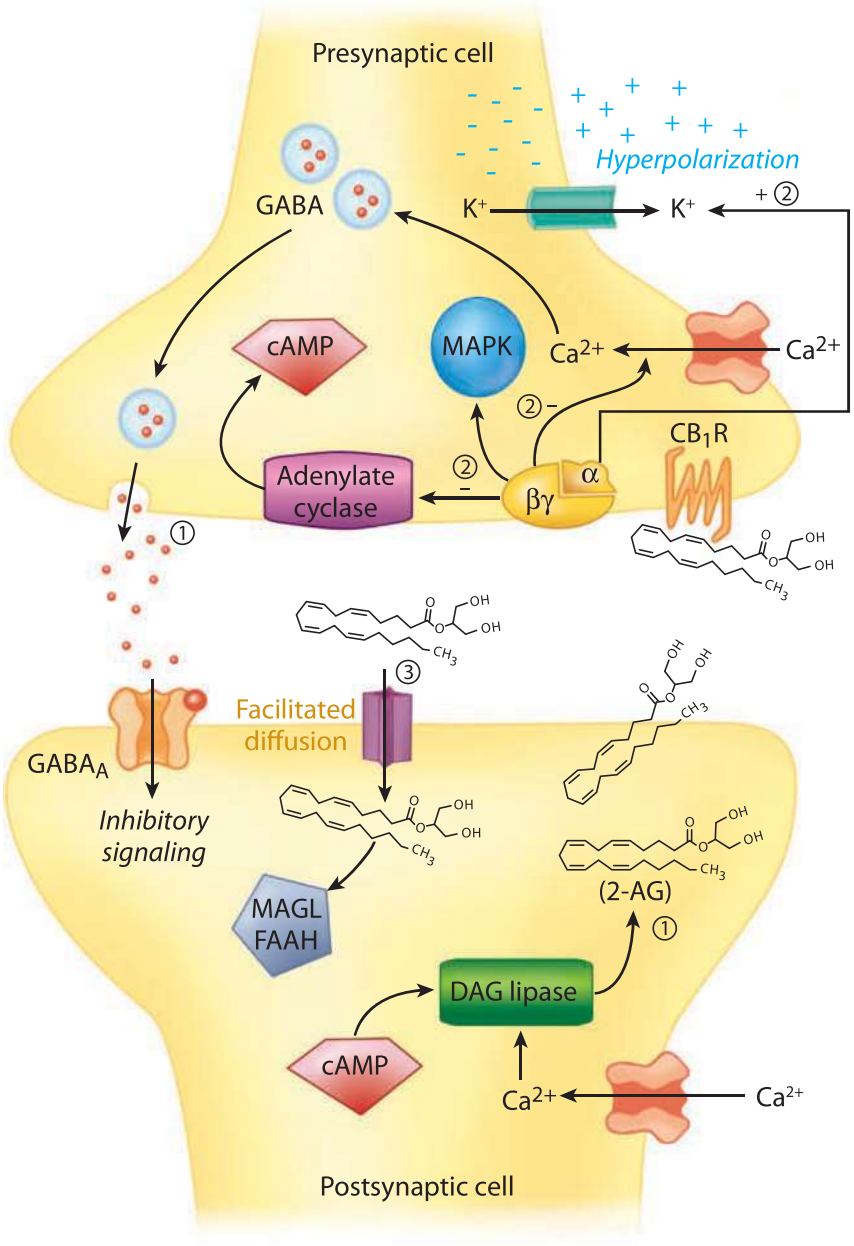

FIGURE 74–2. Endocannabinoids act as allosteric cellular messengers. ① In response to presynaptic γ-aminobutyric acid (GABA) release and postsynaptic binding resulting in increased cyclic adenosine monophosphate (cAMP), endocannabinoids are synthesized on demand and bind to presynaptic cannabinoid receptors. ② Activation of these G protein receptors results in decreased presynaptic adenylate cyclase, decreased cAMP, decreased calcium ion influx, and increased potassium efflux. The net results are hyperpolarization of the presynaptic cell and decreased neurotransmitter release. ③ After binding, endocannabinoids diffuse back to the postsynaptic area, where they undergo degradation by monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH). CB_1R = cannabinoid type $_1$ receptor; DAG lipase = diacylglycerol lipase; MAPK = mitogen-activated protein kinase. 2-AG=2-arachidonoylglycerol. *(Adapted with permission from Seely KA, Prather PL, James LP, et al. Marijuana-based drugs: innovative therapeutics or designer drugs of abuse? Mol Interv. 2011 Feb;11(1):36-51.)*

finishing the cigarette. From 10% to 35% of available THC is absorbed during smoking, and peak serum. Peak serum concentrations depend on the dose. A marijuana cigarette containing 1.75% THC produces a peak serum THC concentration of approximately 85 ng/mL.[63]

Ingestion of cannabis results in an unpredictable onset of psychoactive effects in 1 to 3 hours. Only 5% to 20% of available THC reaches the systemic circulation after ingestion. Peak serum THC concentrations usually occur 2 to 4 hours after ingestion, but delays up to 6 hours are described.[86] Dronabinol has an oral bioavailability of approximately 10% with high interindividual variability.[47,111] Nabilone has an oral bioavailability estimated to be greater than 90% and reaches peak serum concentrations 2 hours after ingestion.[137]

Distribution

Δ^9-Tetrahydrocannabinol has a steady-state volume of distribution of approximately 2.5 to 3.5 L/kg.[47] Cannabinoids are lipid soluble and accumulate in fatty tissue in a biphasic pattern. Initially, THC is distributed to highly vascularized tissues such as the liver, kidneys, heart, and muscle. After smoking or intravenous (IV) administration, the distribution half-life is less than 10 minutes.[64] After the initial distribution phase, THC accumulates more slowly in less vascularized tissues and body fat. Repeated administration of Δ^8-THC (an isomer of Δ^9-THC) to rats over 2 weeks resulted in steadily increasing concentrations of Δ^8-THC in body fat and liver but not in brain tissue. After administration of Δ^8-THC stopped,

the cannabinoids are slowly released from fat stores during adipose tissue turnover.[116]

Δ^9-Tetrahydrocannabinol crosses the placenta and enters the breast milk. Concentrations in fetal serum are 10% to 30% of maternal concentrations. Daily cannabis smoking by a nursing mother resulted in concentrations of THC in breast milk eightfold higher than concomitant maternal serum concentrations; THC metabolites do not accumulate in breast milk.[123]

Metabolism

Δ^9-Tetrahydrocannabinol is nearly completely metabolized by hepatic microsomal hydroxylation and oxidation (primarily CYP2C9 and CYP3A4).[50] The primary metabolite (11-hydroxy-Δ^9-THC or 11-OH-THC) is active and is subsequently oxidized to the inactive 11-nor-Δ^9-THC carboxylic acid metabolite (THC-COOH) and many other inactive metabolites.[1,4,127]

In six volunteers, peak serum THC concentrations occurred at 8 minutes (range, 6–10 minutes) after the onset of smoking, peak 11-OH-THC at 13 minutes (range, 9–23 minutes), and peak THC-COOH at 120 minutes (range, 48–240 minutes) (Fig. 74–3).[63] Approximately 1 hour after beginning to smoke a marijuana cigarette, the THC to 11-OH-THC ratio is 3:1, and the THC to THC-COOH ratio is 1:2; at approximately 2 hours, the ratios are 2.5:1 and 1:8, respectively; and at 3 hours, the ratios are 2:1 and 1:16, respectively.[63] Ingestion of cannabis results in much more variable concentrations and time courses of THC and metabolites (Fig. 74–3). Nonetheless, at 2 to 3 hours after ingestion, the ratios are similar to those after smoking: THC to 11-OH-THC is 2:1, and THC to THC-COOH ranges from 1:7 to 1:14.[165] Δ^9-Tetrahydrocannabinol is detectable in serum 1.5 to 4.5 hours after ingestion of dronabinol.[46]

Of the many aminoalkylindole (AAI) SCs isolated in "Spice" incense blends, human metabolic analyses are only published for JWH-018, JWH-073, and AM 2201.[14,15] In contrast to THC, these cannabinoids are metabolized largely through hydroxylation and oxidation by CYP2C9 and CYP1A2 (with minor contributions of CYP2D6) to active metabolites that retain affinity for and in most are agonists at both CB_1 and CB_2 receptors.[27,28] These metabolites undergo glucuronic acid conjugation in phase II metabolism.

Excretion

Reported elimination half-lives of THC and its major metabolites vary considerably. After IV doses of THC, the mean elimination half-life ranges from 1.6 to 57 hours.[50] Elimination half-lives are expected to be similar after inhalation.[50,63] The elimination half-life of 11-OH-THC is 12 to 36 hours, and that of THC-COOH ranges from 1 to 6 days.[79,165]

Δ^9-Tetrahydrocannabinol and its metabolites are excreted in the urine and the feces. In the 72 hours after ingestion, approximately 15% of a THC dose is excreted in the urine, and roughly 50% is excreted in the feces.[1,21,168] After IV administration, approximately 15% of a THC dose is excreted in the urine, and only 25% to 35% is excreted in the feces.[165] Inhalation is expected to produce results similar to IV administration.[50,63] Within 5 days, 80% to 90% of a THC dose is excreted from the body.[55,68]

Cannabinoids were measured in the urine after smoking a marijuana cigarette containing 27 mg of THC (Fig. 74–3).[94] After smoking THC, urine concentrations peaked at 2 hours (mean, 21.5 ng/mL; range, 3.2–53.3 ng/mL) and were undetectable (<1.5 ng/mL) in five of the eight participants by 6 hours. Urine concentrations of 11-OH-THC peaked at 3 hours (77.3 ± 29.7 ng/mL). The primary urinary metabolite is the glucuronide conjugate of THC-COOH.[170] The urine concentration of THC-COOH peaks at 4 hours (179.4 ± 146.9 ng/mL),[95] and it has an average urinary excretion half-life of 2 to 3 days (range, 0.9–9.8 days).[50] Both 11-OH-THC and THC-COOH remained detectable in the urine of all eight participants for the 8 hours of the study.[94]

After discontinuation of use, metabolites are often detected in the urine of chronic users for several weeks.[39,74] Factors such as age, weight, and frequency of use only partially explained the long excretion period.[39] Primary urinary metabolites of nonclassical SCs are summarized in Fig. 74–4.

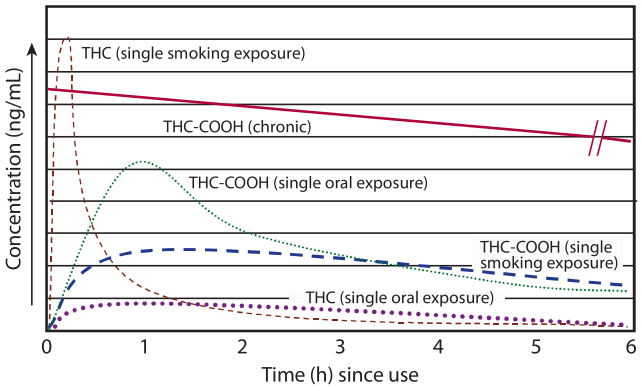

FIGURE 74–3. Estimated relative time course of Δ^9 tetrahydrocannabinol (THC) and its major metabolite in the urine based on the route of exposure. THC-COOH = Δ^9 THC carboxylic acid.

CLINICAL MANIFESTATIONS

The clinical effects of THC use, including time of onset and duration of effect, vary with the dose, the route of administration (ingestion is slower in onset than inhalation), the experience of the user, the vulnerability of the user to psychoactive effects, and the setting in which the THC is used. The concomitant use of CNS depressants such as ethanol or stimulants such as cocaine alters the psychological and physiological effects of marijuana. The therapeutic serum THC concentration for the treatment of nausea and vomiting is greater than 10 ng/mL.[23]

Psychological Effects

Use of marijuana produces variable psychological effects.[40] The variation, which occurs both between and within users, is likely the result of drug tolerance, phase of clinical effects, strain of cannabis, physical and social settings, or user expectations or cognitive capacity. The most commonly self-reported effect is relaxation. Other commonly reported effects are perceptual alterations (heightened sensory awareness, slowing of time), a feeling of well-being (including giddiness or laughter), and increased appetite.[49]

Physiological Effects

Use of cannabis is associated with physiologic effects on cerebral blood flow, the heart, the lungs, and the eyes. In a controlled, double-blind positron emission tomography study,[95] Intravenous THC increased cerebral blood flow, particularly in the frontal cortex, insula, cingulate gyrus, and subcortical regions. These increases in cerebral blood flow occurred 30 to 60 minutes after use and were still elevated at 120 minutes.[96] Similar blood flow changes result from smoking marijuana.[120]

Common acute cardiovascular effects of cannabis use include increases in heart rate and decreases in vascular resistance.[75,148] Cannabis produces dose-dependent increases in heart rate within 15 minutes of using a marijuana cigarette (from a baseline mean of 66 beats/min to a mean of 89 beats/min) that reach a maximum (mean, 92 beats/min) 10 to 15 minutes after peak serum THC concentrations. These changes last for 2 to 3 hours.[8] Increases in blood pressure occur with cannabis use. In a study of six participants, an increase in blood pressure from a baseline mean of 119/74 mm Hg to a mean of 129/81 mm Hg occurred but was not statistically significant.[8] In a double-blind, controlled study of men being investigated for angina pectoris, smoking a marijuana cigarette resulted in statistically significant changes in blood pressure from a baseline mean of 123/79 mm Hg to a peak mean of 132/84 mm Hg.[129] In contrast, in one study, repeated THC use resulted in significant slowing of heart rate (from a mean of 68 beats/min to a low of 62 beats/min) and lowering of blood pressure (from a mean of 116/62 mm Hg to a low of 108/53 mm Hg).[10] Decreased vascular tone causes postural hypotension accompanied by dizziness and syncope.

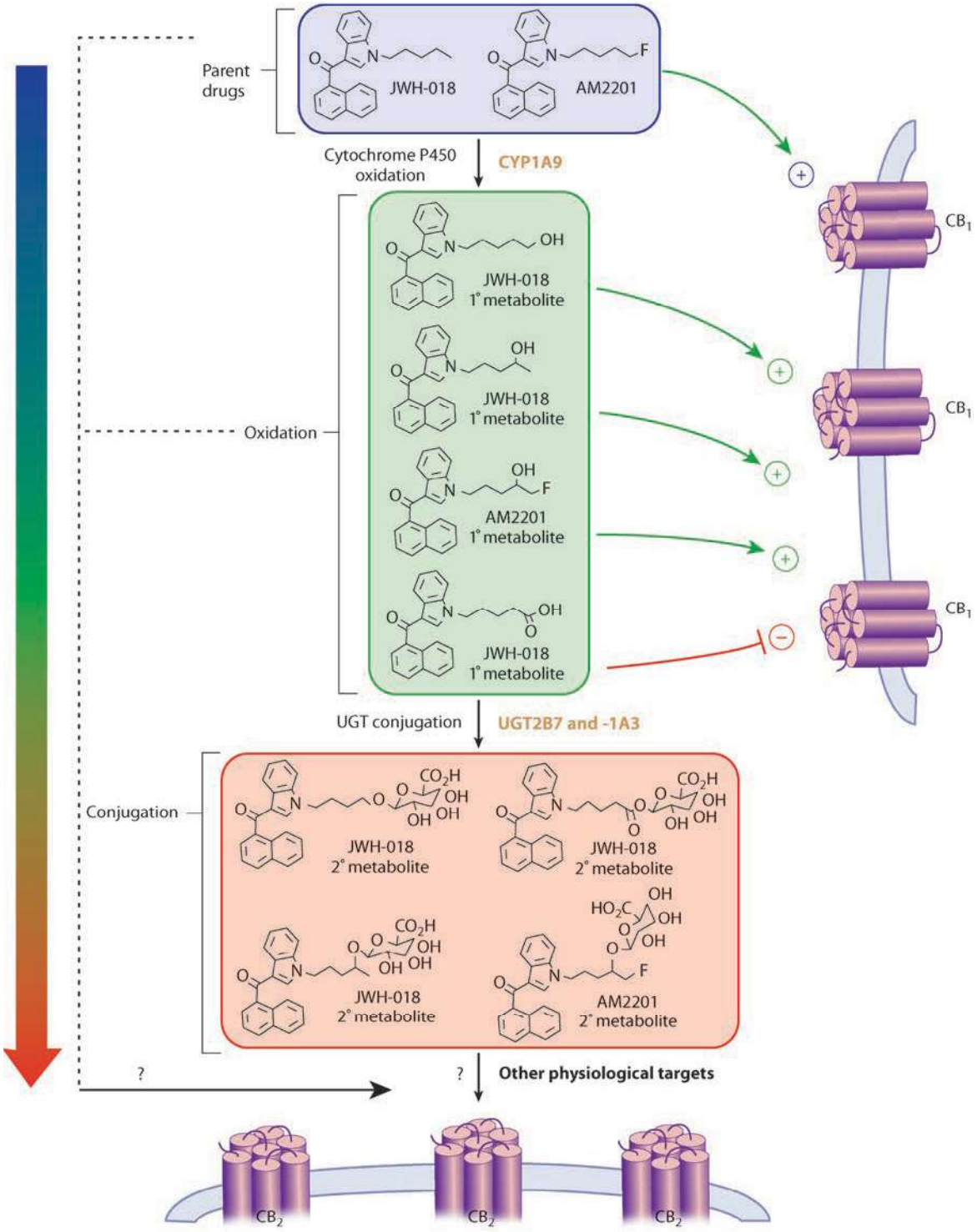

FIGURE 74–4. JWH-018 and AM-2201 metabolism. Aminoalkylindole synthetic cannabinoid JWH-018 and its omega fluorinated analog AM-2201 undergo oxidation by CYP2C9 and CYP1A9 to primary metabolites that retain affinity and ability to bind with cannabinoid receptors. One JWH-018 primary metabolite acts as an antagonist at cannabinoid type 1 receptor (CB_1). Secondary metabolites are formed by conjugation. These metabolites may retain ability to bind to cannabinoid receptors, but at this time it is unclear which do so and in what capacity (agonist, antagonist, or inverse agonist). *(Adapted with permission from Chimalakonda KC, Seely KA, Bratton SM, et al. Cytochrome P450-mediated oxidative metabolism of abused synthetic cannabinoids found in K2/Spice: identification of novel cannabinoid receptor ligands. Drug Metab Dispos. 2012 Nov;40(11):2174-2184.)*

Inhalation or ingestion of THC produces a dose-related short-term decrease in airway resistance and an increase in airway conductance in both normal individuals and individuals with asthma.[156] Smoking marijuana results in an immediate increase in airway conductance, which peaks at 15 minutes and lasts 60 minutes. Ingestion of cannabis produces a significant increase in airway conductance at 30 minutes, which peaks at 3 hours and lasts 4 to 6 hours.[157,158,161] The mechanism for this effect is unclear.

The principal ocular effects of cannabis are conjunctival injection and a transient decrease in IOP. Cannabinoids, applied topically to a rabbit eye, resulted in hyperemia of the conjunctival blood vessels for 2 hours after

application.[103] Regardless of route of administration, cannabis causes a fall in IOP in 60% of users[48] by acting on CB_1 receptors in the ciliary body.[126] The mean reduction in IOP is 25% and lasts 3 to 4 hours.

Physiological effects of novel SCs are not yet studied in any controlled settings.

ACUTE TOXICITY

In addition to the physiological and psychological effects described, acute toxicity includes decreases in coordination, muscle strength, and hand steadiness. Lethargy, sedation, postural hypotension, inability to concentrate, decreased psychomotor activity, slurred speech, and slow reaction time also occur.[115,168]

In young children, the acute ingestion of cannabis is potentially consequential.[93] Ingestion of estimated amounts of 250 to 1,000 mg of hashish resulted in obtundation in 30 to 75 minutes. Tachycardia (>150 beats/min) was found in one-third of the children. Less commonly reported findings include apnea, cyanosis, bradycardia, hypotonia, and opisthotonus.

The acute toxicity profile of nonclassical SCs stands in stark contrast to the relatively mild effects of smoked or ingested phytocannabinoid products. Given the general similarity in receptor binding, both users and clinicians initially expected the effects to be largely identical to marijuana and hashish. The significant differences are likely a result of AAI cannabinoids found in "incense blends" being more potent and efficacious at cannabinoid receptors as well as having active metabolites. Moreover, these products are unregulated, and the presence of additional xenobiotics, such as cathinones, methylxanthines, and long-acting β-adrenergic agonists such as clenbuterol must be considered.

The recent published reports of presumed SC toxicity are challenging to interpret because many lack laboratory confirmation of exposure. In addition, in cases involving "spice" blends, adverse effects may result from the plant matter or adulterants. Finally, the concentration of SCs varies by incense package, even of the same brand and lot, making dose estimation difficult if not impossible.

Agitation[142] and seizures are reported.[85,141] In one report with laboratory confirmation, a patient experienced multiple seizures within 30 minutes after ingesting JWH-018 in powder form.[85] The sample was confirmed as pure JWH-018.

Psychosis (new onset, acute exacerbation of existing psychiatric disorders, and increased risk of psychosis relapse) and anxiety have resulted after a single dose.[57,69,124]

Tachycardia was a common finding detailed in one series, and tachydysrhythmias requiring cardioversion are reported.[85] Chest pain and increased troponin concentrations were observed in three patients who claimed to have smoked spice several days before presenting to the hospital, but laboratory confirmation of SC exposure was not performed.[104]

Diffuse pulmonary infiltrates and dyspnea requiring intubation and mechanical ventilation were reported in a habitual spice user. Laboratory confirmation revealed three parent SCs (AM-2201, JWH-122, and JWH-210).[2]

Accounts of acute kidney injury are described in a case series of 16 previously healthy participants. All patients reported smoking spice incense blends before presentation. The patients had flank pain, nausea, and vomiting with elevated serum creatinine concentrations. Laboratory confirmation was achieved in eight of the patients, and a previously unreported SC was isolated (XLR-11). Several of the patients required hemodialysis, but all eventually recovered.[1]

Cerebral ischemia was reported in a patient using a product confirmed to contain XLR-11. The patient presented after smoking SC with right-sided weakness and later had CT of the brain confirming a left insular stroke. Forensic testing of the product revealed XLR-11, but neither the parent or metabolites could not be identified in the patient's urine, suggesting rapid metabolism.[155]

The fourth-generation indazole derivative SCs were likely responsible for several recent outbreaks of somnolence and bradycardia in suspected users. This stands in contrast to earlier generations of SCs users who presented with sympathomimetic-like symptoms. Patients using nonclassical SCs respond to supportive care.[106]

ADVERSE REACTIONS

Acute Use

Cannabis users occasionally experience distrust, dysphoria, fear, panic reactions, or transient psychoses. Commonly reported adverse reactions at the prescribed dose of dronabinol or nabilone include postural hypotension, dizziness, sedation, xerostomia, abdominal discomfort, nausea, and vomiting. Acute pancreatitis (serum amylase concentration up to 3,200 IU/mL) after a period of heavy cannabis use is reported, but the causal relationship is unclear.[47]

Life-threatening ventricular tachycardia is reported.[132] In six individuals with acute cardiovascular deaths, postmortem whole-blood THC concentrations ranged from 2 to 22 ng/mL (mean, 7.2 ng/mL; median, 5 ng/mL).[5] Although the temporal association is clear, causality is less clear because three of the six people had significant preexisting cardiac pathology. The risk of myocardial infarction is increased five times over baseline in the 60 minutes after marijuana use, but subsequently declines rapidly to baseline risk levels.[105] Atrial fibrillation with palpitations, nausea, and dizziness was temporally associated with smoking marijuana in four patients.[41,83,151]

Chronic Use

Long-term use of cannabis is associated with a number of adverse effects.

Immune System

Cannabinoids affect host resistance to infection by modulating the secondary immune response (macrophages, T and B lymphocytes, acute phase and immune cytokines). However, an immune-mediated health risk from using cannabis was not documented.[81]

Respiratory System

Chronic use of smoked marijuana is associated with clinical findings compatible with obstructive lung disease.[161] Smoking marijuana delivers more particulates to the lower respiratory tract than does smoking tobacco,[171] and marijuana smoke contains carcinogens similar to tobacco smoke. Case reports and a hospital-based case control study suggest that cancers of the respiratory tract (mouth, larynx, sinuses, lung) are associated with daily or near daily smoking of marijuana, although exposure to tobacco smoke and ethanol may be confounding factors.[22,156,159] By contrast a systematic review and a cohort study with 8 years of follow-up demonstrated no association between marijuana smoking and smoking-related cancers,[53,99] and a population-based case-control study found that marijuana use was not associated with an increased risk of developing oral squamous cell carcinoma.[136]

Cardiovascular System

Marijuana use is a risk for individuals with coronary artery disease. An exploratory prospective study of self-reported marijuana use among patients admitted for myocardial infarction found that patients who used marijuana were at significantly increased risk for cardiovascular and noncardiovascular mortality compared with nonusers.[105,111]

Reproductive System

Reduced fertility in chronic users is a result of oligospermia, abnormal menstruation, and decreased ovulation.[18] Cannabis is probably the most common illicit drug of abuse during the reproductive age. No definitive patterns of malformations are recognized.[16] Statistically significant reductions in birth weight (mean, 79 g less than nonusers) and length (mean, 0.5 cm shorter than nonusers) are reported in women who had urine assays positive for cannabis during pregnancy.[163] The results of three other studies are difficult to interpret because marijuana use in pregnancy was poorly documented.[54,173] Epidemiologic studies based on self-reporting of cannabis use

do not support an association between the use of cannabis during pregnancy and teratogenesis.[82,89,173]

The effect of maternal use of cannabis during pregnancy on neurobehavioral development in the offspring was studied. No detrimental effects were reported in children born to women who smoked marijuana daily (more than 21 cigarettes per week) in rural Jamaica.[36] Tremors and increased startling were reported in infants younger than 1 week of age whose mothers used cannabis during pregnancy.[43] These findings, which persisted beyond 3 days, were not associated with other signs of a withdrawal syndrome. There were no abnormalities in the children of parents who used more than five marijuana cigarettes per week in Ottawa, Canada, at 12, 24, and 36 months of age, but lower scores in verbal and memory domains at 48 months of age are reported.[42,44,55] The results of studies evaluating the effect of in utero exposure to cannabis on postnatal neurobehavioral development are equivocal because of methodologic concerns regarding exposure assessment and control of covariates,[33] including the continued parental use of cannabis during the postnatal and early childhood periods. The role of secondhand exposure to cannabis on postnatal and early childhood development of neurobehavioral problems remains unstudied.

Endocrine System

In experimental animals, cannabis exposure is associated with suppression of gonadal steroids, growth hormone, prolactin, and thyroid hormone. In addition, cannabis alters the activity of the hypothalamic-pituitary-adrenal axis.[18] In human studies, the results are inconsistent, long term effects are not demonstrated, and clinical consequences are undefined.[18]

Neurobehavioral Effects

There is a concern that chronic cannabis use results in deficits in cognition and learning that last well after cannabis use has stopped. Neuropsychological tests were administered to 27 adolescents:10 cannabis abusers, 8 infrequent cannabis abusers, and 9 who used no psychoactive substances showed significant differences that persisted for the duration of the study (6 weeks of abstinence) between the cannabis group and the other groups in a visual retention test and a memory test.[145] In a study of three experienced marijuana smokers, arithmetic and recall tasks were impaired for up to 24 hours after smoking.[56] Adults who used cannabis more than seven times per week had impairments in math skills, verbal expression, and memory retrieval processes; people who used cannabis one to six times per week showed no impairments.[11] After 1 day of abstinence, 65 heavy marijuana users (median, use on 29 of past 30 days) showed greater impairment on neuropsychological tests of attention and executive functions than light marijuana users (median, use on 1 day of past 30 days).[125] The authors were uncertain whether this difference was caused by residual THC in the brain, a withdrawal effect from the drug, or a direct neurotoxic effect of cannabis.

There is little evidence that adverse cognitive effects persist after stopping the use of cannabis[72] or that cannabis use causes psychosocial harm to the user.[92] Patients using cannabinoids at younger ages, those using potent cannabinoids such as SCs, and those who have underlying psychiatric disorders are more likely to exhibit psychotic features after cannabinoid exposure.[9,130] An "amotivational syndrome" is attributed to cannabis use. The syndrome is a poorly defined complex of characteristics such as apathy, underachievement, and lack of energy.[26,144] The association of the syndrome with cannabis use is based primarily on anecdotal, uncontrolled observations.[60] Anthropologic field studies, evaluations of US college students, and controlled laboratory experiments have failed to identify a causal rel
e amotivational syndrome.[60] A stud
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chievement" scales in heavy user
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Another study found that behavior that could be interpreted as amotivation was inversely related to the perceived size of the reward.[26]

Abuse, Dependence, and Withdrawal

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, defines marijuana abuse as repeated instances of use under hazardous conditions; repeated, clinically meaningful impairment in social, occupational, or educational functioning; or legal problems related to marijuana use. The amount, frequency, and duration of cannabis use required to develop dependence are not well established.[25,154] Much of the support for cannabis dependence is based on the existence of a withdrawal syndrome. In animals repeatedly given cannabis, the administration of a CB_1 receptor antagonist produced signs of withdrawal.[87,152] In humans, chronic users experience unpleasant effects when abstaining from cannabis.[19] The time of onset of withdrawal symptoms is not well characterized.[18] The most reliably reported effects are irritability, restlessness, and nervousness as well as appetite and sleep disturbances.[152] Other reported acute withdrawal manifestations include tremor, diaphoresis, fever, and nausea. These symptoms and signs are reversed by the oral administration of THC.[9,51] The duration of withdrawal manifestations, without treatment, is not clearly established.[20,152] There are reports of a withdrawal syndrome observed after heavy and prolonged nonclassical SC use.[32, 91,114,139]

Cannabinoid Hyperemesis Syndrome

Chronic, heavy marijuana use is associated with a clinical syndrome (CHS) composed of abdominal discomfort, nausea, and hyperemesis. Symptoms are often refractory to opioids and antiemetics.[166] Patients typically have multiple visits to the emergency department and are subjected to a host of diagnostic and therapeutic modalities ranging from CT scans and endoscopy to cholecystectomy. The hallmark of the syndrome is almost immediate relief of symptoms with bathing or showering in hot water, and a major diagnostic feature is compulsive bathing. The pathophysiology of this syndrome is unclear. In animal models, excessive cannabinoid administration results in downregulation of CB_1 receptors. Endogenous cannabinoids, such as anandamide, demonstrate increased binding affinity for other G protein receptors such as transient receptor potential cation channel subfamily V member 1 (TPRV1).

Relief with hot water may indicate dysfunction of pain perception, excess substance P release, and involvement of TRPV1 which these factors may assist in elucidating the mechanism for this syndrome as well as providing new treatment modalities.[133] This hypothesis is supported by reports of successful treatment of CHS treatment with topical capsaicin. Ultimately, resolution of this syndrome depends on cessation of marijuana use.[3,24,35,45,149,150,166]

Reports also exist of successful CHS treatment with, benzodiazepines, dopamine antagonists, and substance P inhibitors. Opioids are not shown to be effective and are not indicated. Upon discharge, patients should be educated that the syndrome will likely return if the individual continues to use exogenous cannabinoids, and full resolution of symptoms should take place in 10 to 14 days.

CANNABIS AND DRIVING

The perceptual alterations caused by cannabis suggest that its recent use could be associated with automobile crashes. Experimental and epidemiologic studies have provided limited evidence with regard to the effects of cannabis use on driving ability. The published analytical studies of the rela-

risk of causing fatal crashes or serious injuries.[7,119] Regardless, cannabis use decreases reaction times and results in significant driving impairment.[52] One study comparing past driving records of subjects entering a drug treatment center with control participants found that a self-reported history of cannabis use was associated with a statistically significant increase in adjusted relative risk for all crashes (relative risk, 1.49; 95% confidence interval {CI}, 1.17–1.89) and for "at fault" crashes (relative risk, 1.68; 95%CI, 1.21–2.34).[29]

DIAGNOSTIC TESTING

Cannabinoids can be detected in plasma or urine. Immunoassays are routinely available; gas chromatography–mass spectrometry (GC-MS) is the most specific assay and is considered the reference method.

Enzyme-multiplied immunoassay technique (EMIT) is a qualitative urine test that is often used for screening purposes. Enzyme-multiplied immunoassay technique identifies the metabolites of THC. In these tests, the concentrations of all metabolites present are additive. For the EMIT II Cannabinoid Assay, the cutoff concentration for distinguishing positive from negative samples is 20 ng/mL. A positive test result means that the total concentration of all the assayed metabolites present in the urine is at least 20 ng/mL. A positive urine test result for cannabis only indicates the presence of cannabinoids, and it does not identify which metabolites are present or at what concentrations. Qualitative urine test results do not indicate or measure toxicity or degree of exposure. The National Institute on Drug Abuse guidelines for urine testing specify test cutoff concentrations of 50 ng/mL for screening and 15 ng/mL for confirmation.

Variables affecting the duration of detection of urinary metabolites include dose, duration of use, acute versus chronic use, route of exposure, and sensitivity of the method. In addition, factors affecting the quantitative values of urine THC and metabolites include urine volume, concentration, and pH. Using GC/MS, metabolites are typically detected in the urine up to 7 days after the use of single marijuana cigarette.[64,65]

The length of time between stopping cannabis use and a negative EMIT urine test result (<20 ng/mL) depends on the extent of use. Release of THC from adipose tissue is important in drug test interpretation because many chronic users release cannabinoids in quantities sufficient to result in positive urine test results for several weeks. In addition, vigorous exercise stimulates the release of cannabinoids from fat depots. In light users being tested daily under observed abstinence, the mean time to the first negative urine test result is 8.5 days (range, 3–18 days), and the mean time to the last positive urine is 18.2 days (range, 7–34 days).[39] In heavy users (mean, 9 years of using at least once a day) being tested under the same conditions, the mean time to the first negative urine test result (EMIT assay less than 20 ng/mL) was 19.1 days (range, 3–46 days), and the mean time to the last positive urine sample was 31.5 days (range, 4–77 days).[39]

Standard laboratory analyses identify THC and its metabolites but cannot identify the source of the THC (eg, marijuana, hashish, dronabinol). Immunoassays for THC will not identify nabilone because it is not THC; however, nabilone can be specifically identified using high-performance liquid chromatography–tandem mass spectrometry.[146]

Immunoassays give false-negative and false-positive test results (Table 74–1). To help identify evidence tampering, negative urine immunoassays should be accompanied by examining the urine for clarity and measuring urinary specific gravity, pH, temperature, and creatinine[146,163] (Chap. 7).

Immunoassays for THC will not detect nonclassical SCs or their metabolites. Commercial urine immunoassays are available but need to be directed toward a specific nonclassical SCs. High-performance liquid chromatography–tandem mass spectrometry or gas chromatography mass spectrometry are currently the gold standard for laboratory confirmation for SCs, but their clinical utility is limited retrospective confirmation. Further challenges are presented by the multitude of known nonclassical SCs and the rate at which new illicit SCs are introduced to the illegal high market.[49,70,76,78,107,108,135,160,164]

TABLE 74–1 Xenobiotics or Conditions Reported to Produce Inaccurate Screening Test Results for Tetrahydrocannabinol

False Negative[a]	*False Positive*
Bleach (NaOCl)	Dronabinol
Citric acid	Efavirenz
Detergent additives	Ethacrynic acid
Dettol	Hemp seed oil
Dilution	Nonsteroidal antiinflammatory drugs
Glutaraldehyde	Promethazine
Lemon juice	Riboflavin
Niacin	
Potassium nitrite (KNO_2)	
Table salt (NaCl)	
Tetrahydrozoline	
Vinegar (acetic acid)	
Water	

[a]Xenobiotics "possibly" producing false-negative urine test results are usually added to a urine sample, not ingested.

Passive Inhalation

Studies of passive exposure to marijuana smoke and the urinary excretion of cannabinoids have used enclosed spaces with nonsmokers present during and after active smoking by others.[31,86,110,119,122] In an unventilated room (12,225.8 L of air), five adult volunteers were exposed to the side stream smoke of 4 or 16 marijuana cigarettes (THC, 25 mg/cigarette) smoked simultaneously over 1 hour on each of 6 consecutive days.[33] After being exposed to four marijuana cigarettes, four of the volunteers had at least one positive urine by EMIT assay (cutoff, 20 ng/mL) at some unspecified time during the six study days; exposure to 16 marijuana cigarettes resulted in positive EMIT assays only after the second day of exposure.

In a car (1,650 L of air), three adult volunteers were exposed to the smoke from 12 marijuana cigarettes smoked by two people over 30 minutes.[110] Enzyme-multiplied immunoassay technique analyses of urine samples from one passive inhaler were positive at time 0 to 4 hours and on days 2 and 3; a second passive inhaler had one positive urine test result at time 4 to 24 hours after exposure.

Three adult volunteers in an unventilated room (21,600 L of air) were exposed to the side stream smoke of four marijuana cigarettes (THC, 27 mg/cigarette) smoked simultaneously over 1 hour.[112] The concentrations of cannabinoids in urine samples taken 20 to 24 hours after exposure were less than 6 ng/mL when analyzed using radioimmunoassay (RIA) methodology. Another study used an unventilated room (total volume of 27,950 L) containing three desks and a filing cabinet.[86] Over 10 to 34 minutes, each of six volunteers smoked a marijuana cigarette (THC, 17.1 mg/cigarette) and left the room. Four nonsmoking men were in the study room for 3 hours from the start of smoking. The door was opened and closed 18 times during the study. The maximum urine cannabinoid concentration (measured by RIA) in the nonsmokers was 6.8 ng/mL at 6 hours after the start of smoking.

Another study used a closed room (15,500 L of air) with each of four participants smoking two marijuana cigarettes containing 2.5% THC on one occasion and 2.8% THC on a second occasion.[122] On each occasion, two nonsmoking participants were in the room for 1 hour from the onset of smoking. None of the nonsmokers' urine samples (0–24 hours) from either exposure period tested positive on an EMIT assay with a cutoff of 20 ng/mL. An identical experiment in a closed car (~3,500 L of air) resulted in 1 of 23 urine specimens testing positive at 6 hours.

Therefore, passive inhalation of marijuana smoke is unlikely to result in positive urine test results unless the exposure is substantial.

Saliva

Saliva samples are used to establish the presence of cannabinoids and time of cannabis consumption. Cannabinoids (THC, THC-COOH, 11-OH-THC) in saliva are derived from either the smoke of the marijuana or hashish or from a preliminary metabolism in the mouth.[143] Saliva THC concentrations above 10 ng/mL are consistent with recent use and correlate with subjective toxicity and heart rate changes.[101]

Hair

Hair sample analysis is not useful in identifying THC or its metabolites. Only small quantities of non–nitrogen-containing substances, such as cannabinoids, are found in hair pigments.[37,80,102]

Sweat

Perspiration deposits drug metabolites on the skin, and these are renewed even after the skin is washed. Detection threshold is reported to be 10 ng/mL, but forensic confirmation by alternative means is required.[80]

Estimating Time of Exposure

A measurable serum concentration of THC is consistent with recent exposure and toxicity, but there is poor correlation between serum THC concentrations and actual clinical effects.[61] The ratio of THC to THC-COOH is used to estimate time of smoking marijuana. Similar concentrations of each indicate cannabis use within 20 to 40 minutes and imply toxicity. In naïve users, a concentration of THC-COOH that is greater than THC indicates that use probably occurred more than 30 minutes ago. The high background concentrations of THC-COOH in habitual users make estimations of time of exposure unreliable in this population.

Serum concentrations of THC and THC-COOH were used in a logarithmic equation to predict the time since smoking a marijuana cigarette.[94] The ratio provided acceptable results up to 3 hours after smoking (predicted time of exposure averaged 27 minutes longer than actual exposure time), but more than 3 hours after smoking, the predicted exposure time was overestimated by 3 hours. Mean overestimations of predicted exposure time of 2.5 to 4.2 hours for smoking and of 1.6 hours for ingestions are reported when serum samples are taken more than 4 hours after exposure.[63]

Chronic use or oral administration of cannabis increases the concentration of 11-OH-THC relative to the concentrations of THC or THC-COOH. In these cases, estimating time of exposure based on relative concentrations is problematic.[62] In four participants, ingestion of cannabis produced total serum metabolite concentrations less than 20 times the serum THC concentration for 3 hours after ingestion, suggesting that a ratio of this magnitude is consistent with recent oral consumption.[86]

MANAGEMENT

Gastrointestinal (GI) decontamination is not recommended for patients who ingest cannabis products, nabilone, dronabinol, or nonclassical SCs because clinical toxicity is rarely serious and responds to supportive care. In addition, a patient with a significantly altered mental status, such as somnolence, agitation, or anxiety, has risks associated with GI decontamination that outweigh the potential benefits of the intervention.

We recommend that agitation, anxiety seizures or transient psychotic episodes be treated with quiet reassurance and benzodiazepines (midazolam 1–2 mg intramuscularly or diazepam 5–10 mg intravenously) as needed. The management of patients exposed to SCs should not be expected to mirror that of THC or prescription THC-based cannabinoids. Symptomatic and supportive care is often necessary.

Laboratory evaluation should be initiated for signs of electrolyte disturbances and direct toxicity of the CNS, cardiovascular, renal, and musculoskeletal systems. Appropriate crystalloid fluid resuscitation should be given for rhabdomyolysis and acute kidney injury.

Antipsychotics are not recommended at this time during any phase of undifferentiated agitated delirium. If psychotic features persist after the resolution of sympathomimetic features, a quiet space with close observation is indicated, and antipsychotic medications are reasonable if resolution is prolonged. Patients should be observed until asymptomatic.

If available, drug samples in addition to the patient's blood and urine, although not clinically useful, may aid in unknown designer SC identification and understanding of clinical effects.

There are no specific antidotes for cannabis or SC toxicity. Coingestants, such as cocaine, ethanol, designer amphetamines, methylxanthines, and long-acting β-adrenergic agonists, should be identified and their effects anticipated and treated as indicated.

SUMMARY

- Phytocannabinoids were used for centuries both as medicinal substances and as intoxicants.
- Despite the collective human history with cannabinoids, we are only beginning to understand the endocannabinoid system and the consequences of alterations to that system.
- Medical use of THC and smoked marijuana have long existed, and although the safety profile of these xenobiotics is established, evidence of the efficacy of medical marijuana over the gamut of currently prescribed maladies is sparse. Still, the cannabinoid system provides an attractive target for treatment of chronic pain and appetite modulation, but more rigorous and properly designed investigations are needed.
- The toxicity profile of traditional cannabinoids and designer SCs used as drugs of abuse and research chemicals are as different as their chemical structures. Clinicians, users, and public health policy makers alike would do well to separate these groups of cannabinoids in both thought and practice.

Acknowledgment

Michael A. McGuigan, MD, contributed to this chapter in previous editions.

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