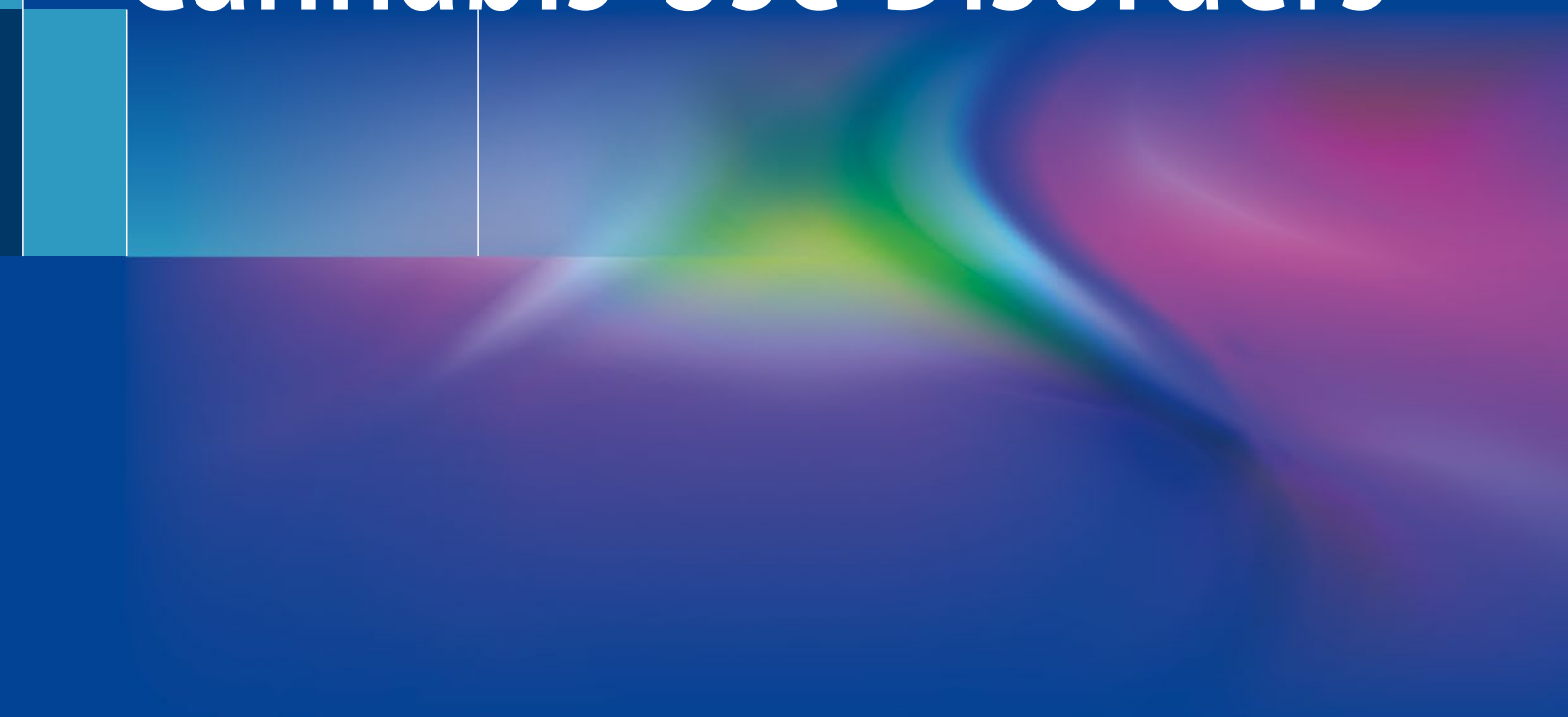
Ivan D. Montoya
Susan R. B. Weiss
Editors

Cannabis Use Disorders



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Foreword

This is a time of significant change around cannabis use, attitudes, and policies in the United States. A growing number of states are loosening restrictions on cannabis sales and use, either by passing medical marijuana laws or by opting to make cannabis legal for adult recreational use. Underlying these changes in state-level drug policy are shifting views of the drug's harms by the public. A large percentage of Americans no longer view cannabis as harmful and favor some form of legalization or decriminalization. Assuming these trends continue, the United States is clearly moving toward having a third legal, addictive substance, one that will most likely become part of an industry that profits from marketing its product to create a cohort of heavy users.

Advocates of legalization see the risks of this trend as minimal, being outweighed by anticipated economic benefits and the scaling back of the costly and discriminatory drug war of the past half century. They often point to the relatively lesser harms associated with cannabis, compared to other illegal substances.

In terms of its capacity to cause death by overdose, cannabis is clearly nowhere near as dangerous as some illicit drugs like cocaine and heroin. Even its very real public safety impacts—for instance on driving—may not be as great as those produced by alcohol. (The jury is still out.) Yet it is easy to forget that alcohol and the other fully legal (for adults) drug, tobacco, are still associated with the greatest health impacts in our society, because their use is so widespread as well as prolonged in many cases. This has a substantial impact on users' (and sometimes others) health, including reduced life expectancy from cancers, heart disease, and in the case of alcohol, liver disease as well. Users of illicit substances—including cannabis, at least historically—tend to stop as they get older, as the risks to employment, family responsibilities, and social opportunities become more relevant. However, it is not known if the legalization of cannabis will result in an increased number of chronic cannabis users and produce a public health impact similar to the other legal substances.

Only time will tell the scope and nature of the health impacts that may arise from new, more prolonged use patterns associated with legal cannabis. Among the most pressing questions are those related to brain development, not only in adolescent and young adult users, but also in children exposed to cannabis prenatally or during lactation, as a result of a mother's cannabis use. But prolonged cannabis use over life may also have impacts on pulmonary, cardiovascular, and neurological health in older individuals that might only become apparent gradually.

Adding to the many unknowns about prolonged use of cannabis is the fact that the product itself is changing. The potency of cannabis purchased illegally and from marijuana dispensaries has increased significantly over the years. It is no longer the same drug that many baby boomers may have used when they were young. The widening variety of cannabis products like edibles and concentrated oils also have diverse effects in the body that are at this point largely unstudied.

The one certainty about cannabis, supported by ample research, and the focus of this book, is its ability to produce a cannabis use disorder (CUD), including addiction. This is an area where public conceptions are starkly out of step with the science. Laypeople may know regular users who claim to be able to stop at any time, or cite celebrities who report using and do not seem to be hindered by cannabis' effects. The latest figures indicate that more than six percent

of the American population may experience a cannabis use disorder in their lifetimes. Among youth in substance use treatment, cannabis is the most commonly reported primary substance of abuse.

This should not be surprising. The active ingredient in cannabis, THC, affects the same reward circuits as other drugs of abuse, and those circuits adapt to the frequent presence of this compound in predictable ways. In many frequent users, it produces tolerance and some degree of dependence; in a certain vulnerable subset of users, it produces a use disorder that can range from mild to severe. One fifth of lifetime cannabis users meet DSM-5 criteria for cannabis use disorders (CUDs); of those, nearly a quarter have a severe disorder. Unfortunately, existing treatments, which are limited to behavioral therapies, are only moderately effective. Therapeutics development, including medications that could augment behavioral treatments, is an active area of research.

We are entering a period of social experimentation, and it is in the nature of experiments that the results are not known at the outset. In such a context, voters, policymakers, health providers, and others are faced with the difficult task of weighing the still-uncertain health and safety impacts of increased cannabis access with various social and economic pressures—for instance, as they decide whether to follow the models of tobacco and alcohol or seek some new regulatory path that places greater restrictions on the cannabis industry's marketing and lobbying power. In these debates, it is important that the science of the health effects of cannabis be accurately characterized and clearly presented.

Bethesda, Maryland, USA Nora D. Volkow

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Introduction to Cannabis Use Disorders

1

Ivan D. Montoya and Susan R. B. Weiss

Introduction

Despite cannabis' status as a Schedule I substance under US federal law, meaning it has a high potential for abuse and no accepted medical use [1], there are a growing number of states that have legalized its use for medical and/or recreational purposes. Twenty-nine states and the District of Columbia (DC) have legalized the medical use of cannabis for a variety of conditions; 8 states plus DC have legalized its recreational use by adults aged 21 or older; and 16 states have more limited medical laws that only permit the use of plants or products containing cannabidiol, a non-psychoactive component of the cannabis plant. States vary in their approaches to legalization, including their regulatory and tax structures, the conditions which qualify for medical use, whether marketing is allowed, and how products are labeled and tested for contaminants, among many other variables [2, 3].

This major change in the cannabis legal landscape did not happen in a vacuum. There have been shifts in public opinion, which have been influenced by many and competing interests. The public health risks of legalizing a third addictive substance have been well articulated by health experts, scientists, and many concerned citizens [4]. However, competing with these views are the potential commercial gains of a burgeoning industry and the recognized disproportionate negative impact prohibition has had on minority populations. Moreover, despite its illegal status, cannabis has always been fairly easy to acquire, resulting in widespread use, especially among young adults. In 2016, 33% of 18–25-year-olds reported past-year use compared to approximately 14% of those 12 and older [5].

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Regardless of where one stands on these issues, we must acknowledge a liberalization of attitudes about cannabis use across much of the country and decreased perceptions of harm among all age groups. Use has been increasing among young (18–25) and older adults (26 and older) and has remained stable overall among younger teens (12–17), while nearly all other drug use has declined in this age group. Approximately 5–6% of 12th graders report daily or near-daily cannabis use, which is likely to lead to disruptions in their academic performance due to lasting cognitive effects among regular users and puts them at increased risk of developing a cannabis use disorder (CUD) later in life [6].

Another concerning trend is the increase in the frequency of use of cannabis. Between 2002 and 2016, the number of past-year users increased from 14.6 million to 24 million; and those using 20 or more days/month increased from 33% to 42% [5]. In addition, the legalization and commercialization of cannabis in the states have led to a tremendous diversity of products (edibles, tinctures, vaping solutions) and very high-potency strains or methods for consuming cannabis. For example, extracts for dabbing can contain 75–80% delta 9-tetra-hydrocannabinol or THC, which is the main psychoactive ingredient in the cannabis plant. We know far too little about the health burdens of these products, since most research, especially on long-term outcomes, involved individuals who used lower-potency cannabis products (4–5% THC in the 1980s and 1990s) [7, 8].

According to the 2016 National Survey on Drug Use and Health (NSDUH), close to 24 million Americans aged 12 and older used cannabis in the past month (37 million used it in the past year), a likely underestimate, since the survey only captures residents of households and other noninstitutionalized individuals. One of the best documented consequences of cannabis' broad appeal stems from its addiction liability: in 2016, close to four million Americans met criteria for CUD, which represents 1.5% of the population aged 12 or older. NSDUH also estimates that approximately 747,000 people in that age group reported cannabis as the substance for which they received the last or current treatment

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in the past year. This number has significantly decreased from 2015, when more than one million people received treatment. This decline may be due to reductions in the perception of risk or problems associated with cannabis use and its increasing social acceptance [9, 10].

CUD is one of the psychiatric diagnoses included in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, of the American Psychiatric Association [11]. It is defined as cannabis use that is associated with clinically significant problems ranging from mild to severe. These may include inability to stop using it despite psychosocial/medical problems, the presence of craving, the need to use larger amounts to obtain the same effect (tolerance), and/or the onset of symptoms when its use is stopped (withdrawal). CUD is part of a larger group of substance-related and addictive disorders, which includes cannabis-induced disorders, such as intoxication, withdrawal, psychosis, and other psychiatric disorders. Although the focus of this book is on CUD, other cannabis-induced disorders are also discussed.

Substance use disorders were first classified independently of other psychiatric disorders in 1980, when the third edition of the *DSM (DSM-III)* was published. The fourth edition of the *DSM (DSM-IV)*, published in 1994, differentiated between cannabis abuse and dependence. The DSM-5 eliminated these categories to include a measure of CUD severity based on the number of diagnostic criteria met by the patient [11]. The DSM-5 diagnostic criteria for CUD now include cannabis withdrawal, which is characterized by irritability that can evolve to anger or aggression, anxiety, restlessness, depressive mood, sleep problems, decreased appetite, and craving. The symptoms typically appear 1–2 days after cessation of chronic cannabis use and may last between 1 and 3 weeks. Sleep disturbances appear to be one of the main reasons why people relapse when they try to quit or reduce cannabis use [12, 13].

The goal of the book is to inform the scientific, medical, and other stakeholder communities about the state of the science related to chronic cannabis use and CUD. Topics covered include patterns and prevalence of cannabis use and disorders (epidemiology) in the United States and internationally; mechanisms by which cannabinoids exert their myriad effects (e.g., the endocannabinoid system); adverse health effects of cannabis use and exposure, including those related to brain development (perinatal and adolescence) and comorbidity; and the continuing need for and development of effective treatments for CUD.

Epidemiology of CUD

The book starts with the chapter by Drs. Lopez and Blanco, which presents a summary of the epidemiology, risk factors, subgroup differences, and comorbidities associated with CUD. It also provides a timely discussion about the continuing evolution of cannabis legislation and how it may have influenced the incidence and patterns of cannabis use and CUD over time.

The next chapter by Drs. Blecha, Lafaye, and Benyamina provides an overview of some of the biological factors associated with CUD and their interaction with environmental variables. It has been reported that about 9–17% of people who have chronic cannabis use may develop a CUD (Volkow et al. 2014). Thus, cannabis use is required but not sufficient to develop CUD. The reasons why people develop CUD are likely to be multifaceted, involving psychological and environmental factors; biological factors, such as genetics and epigenetic modifications; and their interactions, which are discussed in this chapter.

The Endocannabinoid System (ECS)

In the past 30 or 40 years, a large amount of research has been devoted to investigating the biological mechanisms underlying the psychoactive and addictive properties (and other adverse effects) of regular cannabis use. The resulting discoveries have transformed our understanding not only of the cannabis plant and its constituents but also of human physiology. The initial breakthrough came in the mid-60s when Mechoulam and Gaoni identified cannabis' main active ingredient, tetrahydrocannabinol (Δ^9THC), one of more than 100 cannabinoids present in the plant. That led to the discovery of THC's cognate receptors [14, 15].

A few years later, the endogenous cannabinoid ligands anandamide and 2-arachidonoylglycerol (2-AG) were discovered, which revealed an entirely new endocannabinoid signaling system (ECS), consisting of receptors and a dedicated enzymatic machinery that regulates endocannabinoid synthesis and degradation on demand by enzymes such as monoacylglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH). The ECS has been implicated in the modulation of multiple physiological processes, and its discovery has ushered not only a new era in cannabis research but an altogether new field, which is represented here by several authors conveying the excitement over the ECS' translational potential [16]. The chapter by Drs. Kinsey and Lichtman provides a comprehensive account of what the ECS looks like today.

An important component of the marijuana plant is cannabidiol (CBD). It lacks the psychoactive and addictive properties of THC and has very low affinity for the cannabinoid (CB) receptors in the brain. Studies suggest that CBD has anxiolytic, antidepressant, and antipsychotic-like effects and neuroprotective properties. It appears that CBD may also have some potential therapeutic effects against CUD. The chapter by Drs. García-Gutiérrez, Navarrete, Viudez-

Martínez, Gasparyan, Caparrós, and Manzanares reviews the effects of CBD and presents results showing that it may reduce the behavioral disturbances associated with cannabinoid withdrawal, suggesting the need to further evaluate it in clinical trials for this indication.

Chemists have taken advantage of the ubiquitous actions of the endocannabinoid system to design and synthesize molecules that target the receptors or enzymes involved in this system. The chapter by Drs. Janero, Vemuri, and Makriyannis describes new candidate chemical agents that target the endocannabinoid system with the goal of developing safe and effective medications to treat different aspects of CUD, such as cannabis overdose, withdrawal, and addiction.

Translational Aspects

One of the main challenges in the discovery and development of medications to treat CUD or any other disorder is reaching the point where the new compound is allowed by the Food and Drug Administration (FDA) to be tested for the first time in humans for a clinical indication. The chapter by Dr. Hampson and Mr. Walsh presents some insight about the translational process of bringing a new compound from preclinical testing to clinical evaluation for a CUD treatment indication.

Preclinical research in animals has been instrumental in understanding the neurobiology of CUD and thus the development of safe and effective medications to treat this disorder. Studies in animals have shown that acute administration of THC can elicit the release of dopamine, the main neurotransmitter in the brain reward system like other drugs of abuse [17, 18]. Animal models of different aspects of CUD have been established. They include cannabis self-administration, conditioned place preference, and drug discrimination. These studies in animals have provided evidence of the addictive effects of THC. One of the most valuable applications of animal models of CUD is the ability to determine the effect on those models of different potential pharmacotherapies for CUD [19–22]. The chapter by Dr. Zuzana Justinova provides a description of the animal models that are currently available for the evaluation of the of rewarding, relapse-inducing, subjective, and other abuse-related effects of cannabinoids and some of the findings of studies of medications tested for CUD in these models.

Cannabis use and CUD may include a constellation of clinical signs and symptoms, and, likewise, the goals of its treatment depend on the clinical needs of the individual. Human laboratory studies have been instrumental in understanding the psychophysiological effects of cannabis, the progression from cannabis use to CUD, and testing the safety and efficacy of potential treatments for CUD prior to conducting large-scale clinical trials. Some of these studies involve the administration of cannabis products to humans under strict medical safety and ethical protections and careful and controlled conditions. The chapter by Drs. Arout, Herrmann, and Haney provides an overview of the methods used to evaluate cannabis use features such as intoxication, positive reinforcing effects, tolerance, withdrawal, abstinence initiation, and relapse under carefully controlled human laboratory conditions. The chapter also provides a summary of results obtained from testing medications to treat CUD.

Clinical Manifestations

The chapter by Drs. Budney, Borodovsky, and Knapp offers a complete description of the clinical manifestations of CUD, and, as with other substance use disorders, those with this disorder commonly present other co-occurring psychiatric disorders that further complicate the clinical treatment of CUD. An important aspect is the withdrawal syndrome, which is characterized by behavioral, somatic, and mood symptoms, which often contribute to cannabis use relapse. This syndrome is the result of changes in the endogenous cannabinoid system after cessation of chronic cannabis use, which also shows important gender differences. The chapter by Drs. Schlienz and Vandrey provides a comprehensive review of the etiology, clinical characteristics, and gender differences in cannabis withdrawal.

The increase in cannabis use and in cannabis potency and new routes of administration, along with the emergence of highly potent synthetic cannabinoids, have resulted in greater numbers of calls to poison control centers and visits to emergency departments due to cannabis intoxication and nonfatal overdose. It has been reported that the highest incidence of adverse events occurs in states with permissive cannabis laws, often involving children and domestic pets that accidentally ingest cannabis products [23–25]. The effects of cannabis depend on the route of administration, the amount of cannabinoid that reaches the brain, and the individual characteristics of the consumer. Symptoms may include tachycardia, nausea and vomiting, cognitive and motor impairment, injected conjunctiva, anxiety and panic-like symptoms, or even severe psychosis. Unfortunately, there is currently no antidote available; thus, treatments are limited to general measures to stabilize the patient and ancillary medications such as anxiolytics or antipsychotics [26]. Luckily, deaths related to cannabis overdose, without other substance used, are rare. The chapter by Drs. Cooper and Williams gives an overview of the factors associated with the increase in cannabis intoxication, its clinical manifestations, and some suggestion about its treatment.

The appearance in the markets of products containing synthetic cannabinoids has significantly changed the clinical landscape of cannabinoid-related adverse events. They vary widely in content and concentration of cannabinoids, and their psychoactive and physiological effects are often much stronger than those of cannabis [27]. The chapter by Drs. Karila and Benyamina provides a summary of the effects and consequences of synthetic cannabinoids in humans.

There has been a fair amount of debate about the interaction between CUD and other psychiatric disorders. It has been reported that the prevalence of psychiatric disorders among individuals with CUD ranges from 8% to 40%. Conversely, the prevalence of CUD among individuals with psychiatric disorders ranges from 4% to 16%. The highest prevalence of CUD is among individuals with schizophrenia. There are multiple hypotheses about the reasons for this association but none is conclusive [28–31]. Unfortunately, there are no effective treatments for CUD and psychiatric comorbidity. Most treatments focus on targeting the psychiatric disorder. Dr. David Gorelick's chapter reviews the epidemiology of these comorbid conditions, their risk factors, and treatments that have been investigated.

Given the high relevance of comorbid CUD and psychotic disorders, the chapter by Drs. Tikka and D'Souza provides a comprehensive review of the association between cannabinoids and psychosis. They report that cannabis use can be associated with psychosis not only soon after exposure but that it can also last beyond the period of intoxication. This association appears greater with earlier age of exposure, longer durations of use, and genetic vulnerability. They propose that cannabinoids are a "component cause" interacting with other genetic or psychosocial factors to result in psychosis.

In addition to CUD and psychiatric comorbidity, regular use of cannabis has been associated with other medical consequences. Few associations have been unequivocally established due to the multiple confounding variables. For example, while smoking cannabis may be a risk factor for the development of lung cancer, this has been difficult to prove because of the common co-use of tobacco products among long-term cannabis users [4]. It has also been suggested that chronic cannabis use is associated with cardiovascular risks, including ischemic stroke [32, 33]. The chapter by Drs. Khalsa and Baler reviews the state of the science, identifies key knowledge gaps, and highlights important areas for future research.

Developmental Aspects of CUD

Considering these remarkable advances in cannabinoid science, the ability of cannabis to cause addiction is anything but surprising. Animal studies have established that acute administration of THC can elicit the release of dopamine, the main neurotransmitter in the brain reward system and a powerful conditioned reinforcer of the pleasurable effects of drugs of abuse, including THC. The factors that modulate interindividual differences in the risk of developing CUD are only partially understood. This is a very active area of research that involves investigations into the same biological, environmental, and social determinants that modulate the risk of other complex biobehavioral disorders [34]. The developmental nature of the addictive process is particularly worrisome in this context, since we know that adolescents are more likely to consume cannabis and are also more vulnerable to the risk of developing CUD.

An increasing public health concern is the use of cannabis during the perinatal period. Cannabis use in pregnant and postpartum women is increasing, while their perception of risk for themselves and the unborn fetus is decreasing. Unfortunately, THC crosses the placental barrier and reaches the brain of the fetus. Given the mechanism of action of cannabis on the endocannabinoid system and the role of this system on the developing brain of the fetus, there is reason to suspect cannabis exposure portends harm to the fetus and the child. Moreover, THC is also present in breast milk, thus children breastfed by a mother who uses cannabis may suffer some effects of THC exposure. Currently, the American College of Obstetricians and Gynecologists recommends advising pregnant women and women contemplating pregnancy about potential risks of prenatal marijuana use and discourages its use during this period [35]. The chapter by Drs. Velez, Jordan, and Jansson provides a comprehensive review of the current knowledge about epidemiology of perinatal cannabis use, the effects of cannabis exposure on the fetus and child, and some therapeutic strategies for the mother-child dyad affected by cannabis use.

As noted above, adolescents are particularly vulnerable to consume cannabis and to develop CUD. There are multiple theories to explain this. Notably, of the 747,000 people who received treatment for CUD in the United States in 2016, approximately 200,000 were between the ages of 15 and 25 [5]. While, not all treatment may be voluntary (i.e., some is court-mandated), it is clear that young people are affected by their cannabis use, and many have difficulty quitting. There are significant concerns about the sequelae on the brain of adolescents because the brain is still maturing and the endocannabinoid system plays an important role in its development [34]. Some of the consistently reported consequences of heavy use by adolescents are poor educational outcomes, sustained cognitive impairment and lower IQ, and lower life achievement. However, these effects are difficult to separate from other psychosocial risk factors and other drug use [4]. To evaluate the effects of cannabis on the developing brain of adolescents, the National Institute on Drug Abuse (NIDA), in collaboration with multiple other NIH Institutes and Offices, is supporting the Adolescent Brain Cognitive Development

(ABCD) Study, a longitudinal study that is following approximately 11,500 children beginning at ages 9–10 for 10 years into early adulthood [36]. Participants are undergoing a battery of brain imaging and extensive psychosocial and neurocognitive testing to examine how multiple interacting factors (including substance exposure) affect development. The chapter by Drs. Tomko, Williamson, McRae-Clark, and Gray discusses the age-related trends associated with CUD, the neurobiological risk factors of CUD in adolescents, and the behavioral and pharmacological treatments for adolescents with CUD.

Treatment

Approximately one quarter of individuals with CUD receive treatment for the disorder [5, 34]. This may involve pharmacological or non-pharmacological interventions. Disappointingly, there are no medications currently approved by the FDA for the treatment of CUD, although not for lack of trying. Multiple medications have been investigated. Following up on the significant advances in our understanding of the ECS, both cannabinoid agonists and antagonists have been evaluated for this purpose. The chapter by Drs. Brezing and Levin presents an overview of the cannabinoid agonists, partial agonists, and antagonists for the treatment of CUD. Another approach has involved investigations of the safety and efficacy of neurotransmitter and neuropeptide targets, which is discussed in the chapter by Drs. Sherman and McRae-Clark. They present potential pharmacotherapeutic agents, including those that exert their action on the serotonergic, dopaminergic, and the oxytocinergic systems. The chapter by Dr. Barbara Mason provides a review of the evidence for the efficacy and safety of anticonvulsants such as divalproex sodium, gabapentin, and topiramate for reducing cannabis use and withdrawal symptoms.

Another important strategy for the development of medications to treat CUD is the investigation of prodrugs as potential therapeutic agents. Prodrugs undergo in vivo transformation to become pharmacologically active and offer the prospect for improved stability, absorption, and/or penetration when limitations exist in the pharmacokinetics of the active compounds. The chapter by Dr. Kevin Gray presents results from studies with N-acetylcysteine (NAC), a prodrug of the amino acid cysteine, that was shown to reduce cannabis seeking and reinstatement in animal models of relapse. The results of the clinical studies are not conclusive but are sufficiently promising to deserve continued evaluation.

Non-pharmacological interventions are available and routinely deployed in the field; the most commonly used are cognitive behavioral therapy, motivational interviewing, cognitive enhancement, and contingency management [37]. The latter appears highly efficacious at reducing cannabis use and improving treatment adherence, although long-term abstinence is uncommon. The chapter by Drs. Aklin and Bedard-Gilligan provides a review of the behavioral treatments for CUD and offers some suggestions for improving treatment outcomes and for future research directions. And because of the increasing evidence and relevance of mindfulness-based interventions, the chapter by Dr. David Shurtleff provides a timely overview of complementary medicine's mindfulness-based practices for CUD. It is suggested that many symptoms associated with CUD, for example, those related to cannabis withdrawal – irritability, anger, anxiety, restlessness, etc. – may be susceptible to improvement with mindfulness techniques. This chapter also provides the conceptual framework and neurobiological mechanism of meditation practices as well as their application in treatment and prevention of CUD.

Unfortunately, and as documented in various chapters, there are still no FDA-approved medications for CUD, and behavioral interventions are only moderately effective. However, many thousands of patients need treatment each year for cannabis-related problems. Their reasons for accessing treatment vary (some are judicially mandated), and we have insufficient knowledge about the kind of treatment they receive or how (if) it is reimbursed. The chapter by Drs. Kiselica and Duhig offers an overview about access to and reimbursement for CUD treatments, including the opinion of treatment payers.

The final chapter written by experts on CUD from several countries (Drs. Gust, Ahumada, Copeland, Griffiths, Howard, and Hynes) offers a perspective about the international aspects of cannabis use and CUD. They remind us that cannabis is the most prevalent illicit drug used in the world and summarize the epidemiology of cannabis use across large swaths of the world. They emphasize the potential lack of comparability of data from other countries with data from the United States, which uses the CUD diagnostic criteria as defined by the DSM-5, while most countries use the International Classification of Diseases (ICD) of the World Health Organization (WHO). The WHO is working on the 11th edition of the ICD, and the hope is that the diagnostic criteria for CUD and other mental disorders will be more comparable.

Conclusion

Given the high prevalence of cannabis use, its addictive liability, the large number of people who report cannabis as the substance for which they receive treatment, and the mounting evidence that chronic cannabis use is associated with changes in the brain as well as neurobehavioral and medical consequences, it is imperative to consider CUD is a public health problem that needs to be studied and properly addressed. Scientific advances are offering extraordinary opportunities for the development of effec-

tive CUD interventions, both in the prevention and treatment arenas. They include dramatic advances in our understanding of how the ECS, other neurotransmitters and brain circuits, and a long list of interacting risk and protective factors influence the onset and progression of CUD. We hope this book offers to the readers the state of the science of CUD, the gaps and opportunities to advance this science, and useful insights for future research directions.

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Epidemiology of Cannabis Use Disorder

2

Marsha Lopez and Carlos Blanco

Introduction

The goal of this chapter is to provide an overview of the epidemiology of cannabis use disorder (CUD). To do so it must address the three primary components of that term: epidemiology, cannabis use, and disorder. Often considered the foundation of public health research, *epidemiology* is the study of disease in a population (literally the study of epidemics). It gathers information about a population's experience by examining the occurrence, patterns, and distribution of a condition, most often through survey research. Taking into account temporal, social, environmental, genetic, and other potential mechanisms, epidemiologic research is used to answer questions that can only be addressed outside the laboratory or clinical setting, to gain understanding of who within a population may be at increased or decreased risk for any particular disorder, in this case CUD, and why some groups may experience certain health outcomes while others do not. Epidemiologists conduct population-based surveys based on the premise that there are certain predisposing characteristics toward health problems, asking questions about drug experiences along with a variety of personal and environmental factors such as age, race/ethnicity, marital status, poverty level, employment, and others that interact with behaviors across development and may influence health outcomes. These studies can examine the landscape of cannabis use within and across groups, and over time, and use this information to determine the associations between potential causal factors and disease or between interventions and outcomes. Multiple methods and approaches are required in epidemiologic research as methodological differences in how the subjects are selected, how and where the questions are asked, and even in what order can play a part in how the participants respond. Consistency in patterns and results across methods lends confidence to our understanding of findings. Two of the most frequently used approaches to describe the frequency of outcomes are prevalence and estimates of association or risk. Prevalence is the proportion of people within a population who have the condition of interest. Estimates of risk can be derived from statistical associations between a variable we call a risk or protective factor and cannabis dependence. Neither of these necessarily speaks to a causal relationship, but ratios of disease rates can estimate the strength of an association which can spur research to determine causality.

There have been many vehicles for measuring *cannabis use* at a population level over the years, but some of the most established and ongoing have been the Monitoring the Future Study [1] and Youth Risk Behavior Survey [2] for studying youth, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) for adults, and the National Survey on Drug Use and Health (NSDUH), previously known as the National Household Survey on Drug Abuse, for youth and adults. These surveys vary in terms of whether they are cross-sectional or longitudinal in nature, but they are all nationally representative of their respective populations. There exist many other studies with epidemiologic samples that represent local areas and more defined populations. Cannabis use is a necessary but not a sufficient requirement for a diagnosis of cannabis use disorder (CUD), and epidemiologic research seeks to understand why some who use make the transition to problematic use or CUD and others do not. Often the smaller studies allow for the more rigorous assessment needed to make a diagnosis of substance use disorder, but among the national surveys, the NSDUH and NESARC have incorporated reliable and valid instruments that provide a diagnosis of CUD and around which this chapter is framed. Although some of the survey research uses the term marijuana and others cannabis, for the purposes of this chapter, "cannabis" will be used as a universal term across all sources.

The existence of cannabis use *disorder* (CUD) historically has been a topic of some controversy, as early versions of the DSM separated cannabis from other substance use disorders [3] although modern scientific research has con-

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sistently shown use can lead to the development of problems and disorder among a subset of users [4]. CUD is generally understood as abuse or dependence, terms defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The identification of CUD in the DSM, the standard mental health diagnostic tool for clinicians, has evolved over its different editions. Early versions of the DSM characterized substance use disorders as symptoms associated with other disorders, such that they were secondary to other psychiatric conditions, and not until DSM-III in 1980 were substance use disorders classified independently. Subsequent versions have sought to improve nosology by better classifying substance use disorders and by distinguishing between abuse and dependence in DSM-IV which was published in 1994 and remained in use through 2013. DSM-V, published in 2013, shifted away from the abuse/dependence paradigm toward a more dimensional scale that incorporates level of severity into its measurement of the syndrome, essentially combining the abuse and dependence criteria into one set for a diagnosis of disorder. Both DSM-IV and DSM-V include some combination of the following clinical features: hazardous use (e.g., driving while intoxicated), social/interpersonal problems related to use, neglected roles, tolerance, use of larger amounts/for longer than intended, repeated attempts to quit or control use, a lot of time spent using, physical/psychological problems related to use, and activities given up to use. DSM-IV also included legal problems as part of the diagnostic criteria, whereas DSM-V removed legal problems altogether but includes craving as possible features. Table 2.1 outlines the differences between the two models of CUD [5]. The repeated changes in the diagnostic criteria are the comparability of research results, as the prevalence of disorder can change with the definition, even when using the same data. Although some emerging research has incorporated the more recent DSM-V, the majority of published survey research on CUD refers to the DSM-IV version. Therefore that will be the focus of the estimates presented.

Table 2.1 Caption

A maladaptive pattern of use leading to clinically significant impairment or distress, as manifested by the following within a 12-month period	DSM IV abuse[a] or dependence[b]	DSM 5 CUD[c]
Recurrent use resulting in failure to fulfill role obligations at school, work, home	A	X
Recurrent use in physically hazardous situations	A	X
Recurrent substance-related legal problems	A	
Continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by cannabis use	A	X
Tolerance (marked increase in amount; marked decrease in effect)	D	X
Characteristic withdrawal symptoms; substance taken to relieve withdrawal		X
Substance taken in larger amount and for longer period than intended	D	X
Persistent desire or repeated unsuccessful attempt to quit or reduce use	D	X
Much time/activity to obtain, use, recover	D	X
Important social, occupational, or recreational activities given up or reduced	D	X
Continued use despite adverse consequences	D	X
Craving		X

[a]One or more criteria for abuse
[b]Three or more or more criteria for dependence
[C]Two or more criteria for SUD

US Estimates and Trends

National Surveys

The first step in determining how CUD impacts public health is to estimate who, or what proportion of the population, meets the criteria for a CUD. The United States relies on national surveys to estimate the prevalence of CUD at the overall population level. The two most widely used surveys are the National Survey on Drug Use and Health (NSDUH, formerly the National Household Survey on Drug Abuse) and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). The NSDUH is an annual cross-sectional survey of roughly 70,000 individuals ages 12 and older living in civilian US households. It captures information on current use, perceived risk, availability, and current DSM-IV abuse, dependence, and CUD [6]. The survey has undergone many revisions since its inception in 1971. This can complicate examination of trends over time as assessments change, but the current version of cannabis assessment has been consistent since 2002 so CUD trends can be studied using that year as the baseline. The NESARC is a set of nationally representative surveys each of around 35,000 civilian adults ages 18 and older residing in households and group quarters. The NESARC survey, which had a longitudinal design, collected the first wave of data in 2001–2002 and its second wave in 2004–2005. The NESARC III (2012–2013) was cross-sectional, and despite its name, it examined a sample that was completely independent from the sample studied in the NESARC Waves 1 and 2. The NSDUH survey is conducted as a self-report assessment, whereas the NESARC assessments are conducted by trained interviewers.

Prevalence and Trends in Cannabis Use

The 2016 NSDUH estimates that nearly 24 million Americans ages 12 and older are current cannabis users, defined as any use in the past month. This represents close to 9% of the household population in that age range. There has been an overall upward trend since 2002, which appears due to an increase in adult use, i.e., in the age groups 18 years and older. Among youth ages 12–17, the trend has been decreasing over the same time frame, from 8.2% reporting current use in 2002 compared to 6.5% in 2016. Over 7% of adults ages 26 and older reported current cannabis use, up from 4% in 2002, but young adults have a substantially higher prevalence of use, with about 1 in 5 people ages 18–25 reporting they are current cannabis users (20.8%) [6]. Among respondents who reported past year cannabis use in NESARC Wave 1 in 2001/2002 and those in NESARC III in 2012/2013, the prevalence of cannabis use more than doubled from 4.1% to 9.5% [7]. The NESARC does not include youth, but across all age groups 18 years and older, increases in reported cannabis use were seen between 2001/2002 and 2012/2013.

Prevalence and Trends in Cannabis Use Disorder

Disorder is defined as meeting the DSM-IV criteria for cannabis abuse or dependence (CUD). The NSDUH estimated that in 2016, about four million people met the criteria for CUD, corresponding to 1.5% of the US population ages 12 and older [6]. According to the NSDUH, there has been an overall decreasing trend of CUD since 2002 [6, 8], particularly among youth. In 2016 2.3% of 12–17-year-olds who had reported cannabis use in the year prior to the survey were classified as having a CUD, down from 4.3% in 2002, whereas among adults ages 26 and older, there has been no change since 2002 [6]. Among daily or almost daily cannabis *users*, the prevalence of CUD has also decreased in all age groups over the same time period [6].

Unlike the trend reported by NSDUH, NESARC found an increase in CUD overall between the two surveys from 1.5% to 2.9%, [7]. Although the reasons for these differences between surveys are not well understood, they may be due at least in part to the fact that the NESARC does not include youth, who saw the steepest decrease in NSDUH. The prevalence of CUD among past year cannabis *users*, on the other hand, decreased from 35.6% to 30.6% during the same time frame, suggesting there is an increase in prevalence of users overall but not an increase in risk of CUD among users. In other words, although there was no increase in the risk for developing CUD among cannabis users, there were a larger number of people at risk for CUD, and therefore a greater proportion of the general population developed CUD.

Risk Factors

As noted above, nearly one third of adult recent cannabis users in the United States may meet at least one criterion for CUD, and over the course of a lifetime, about 9% of people who ever use cannabis will develop a CUD (i.e., either abuse or dependence) [9, 10]. One of the primary answers sought in the epidemiology of CUD is among those who use, which individuals will develop problems. Many factors have been identified as contributing to the risk for developing CUD, and this body of research is evolving as the state of cannabis, and cannabis use is also evolving in contemporary times. One of the factors linked to risk of developing CUD has been younger age of onset of use. Youth under the age of 18 are four to seven times more likely to develop cannabis disorder than adults [11, 12]. Whether this risk is a result of the actual substance use at an earlier age or if the CUD is part of the same underlying predisposition that lead to the early drug initiation continues to be the subject of debate, but independent of the mechanism, it is clear that adolescence is a particularly vulnerable period for developing any substance use disorder. Other factors associated with the development of CUD involve biological pathways (e.g., genetic vulnerability); familial and peer environments, including family structure and parental attachment; patterns of cannabis use and other drug use; behavioral disinhibition; and certain psychiatric and personality disorders, among others [13–18]. Successful prevention programs aim to mitigate these risk factors, although evidence suggests combinations of both biological and environmental factors contribute to risk for CUD, and similar patterns also can contribute to likelihood of remission. Being female, being younger, and having a lifetime diagnosis of conduct disorder all predicted remission from cannabis disorder, while those having a personality disorder or diagnosis of another substance use disorder were less likely to remit [19].

Subgroup Differences

Drug use disorders can disproportionately impact certain groups of the population, and identifying those segments of the population and understanding why they may be at greater risk can help in prevention and treatment efforts. Gender, race/ethnicity, sexual minorities, veterans, and other sociodemographic characteristics like geography, employment, education, poverty, and marital status may influence risk for CUD, through either biological mechanisms or socioeconomic risk factors such as access to care or neighborhood disadvantage.

More men than women report using cannabis, and substance use disorders are more likely to be reported by men as

well. Among adult cannabis users, men were more likely to report CUD than women, and those respondents who self-identified as White were less likely to meet the criteria for CUD than most other race/ethnicities [7]. Advanced education beyond high school and full-time employment were associated with lower risk [7, 20], whereas lower income and having never been married were associated with an increased likelihood of CUD [7, 21]. There is some evidence that men tend to start using cannabis at an earlier age than women and are more likely to transition to CUD [9], but among users women transition to CUD more rapidly than men [21, 22]. Cannabis users who identify as American Indian/Alaska Native were more likely to transition to CUD compared to White cannabis users.

Psychiatric Comorbidity

Although drug use and disorder, including cannabis use and CUD, are often discussed and classified around an individual substance or disorder, they often co-occur with other psychiatric disorders, including other substance use disorders. Cannabis use and CUD have been associated with comorbid mood disorders, anxiety disorders, and psychosis, among others [23–27]. Associations of CUD with alcohol and nicotine use disorders were found in both the NSDUH and NESARC. In the latter they were also associated with mood, anxiety, personality, and post-traumatic stress disorders. Most of those disorders are not specifically assessed in the NSDUH [28, 29]. The questions of whether the conditions stem from the same etiology or are caused by or in response to one another is the topic of continued investigation, which in the epidemiologic realm can be partially addressed with longitudinal studies [30]. The NESARC Waves 1 and 2 were administered 3 years apart and therefore allow to examine prospectively at the associations between cannabis use, CUD, and other psychiatric disorders [26, 31]. There is some evidence that once other factors are taken into account, cannabis use is associated with an increased risk for other substance use disorders but not mood or anxiety disorders [26], although studies have been mixed as some have suggested a common underlying cause for CUD and depression and yet others a possible causal association between CUD and mood disorder [31].

Research has explored the relationship between cannabis use and/or CUD and psychosis such that there appears to be agreement of an association: however, that relationship has been tied primarily to high-risk groups or high-frequency or THC cannabis use [31, 32]. This finding is particularly significant in the current cannabis market which has an increasing variety of strengths and modes of consumption as state legalization policies proliferate across the United States [33].

Impact of Cannabis Policy

No current discussion of cannabis use or CUD trends can discount the relatively recent implementation of state cannabis laws. How these laws have influenced trends in cannabis use and CUD has been of great interest to the biomedical community. The landscape of cannabis policy started evolving in 1996 when California became the first state to pass a medical cannabis law, and there has been an acceleration in that evolution over the past 5–10 years, in particular with varying state policies that now cover cannabis use for both medical and recreational purposes. As policy changes are quickly evolving, the research in this area is just emerging. Early findings suggest a greater relative increase in CUD in those states that adopted medical cannabis laws compared to those that have not [5], although there is some evidence that the risk of developing CUD among users does not differ between states that have cannabis policies vs. those that do not [34]. Nevertheless, little is known about the effects of recreational cannabis laws on risk of CUD, and continued research in this cannabis policy realm is warranted. The possible mechanisms for how changes in policy could influence cannabis use and CUD are diverse and range from socioenvironmental exposures such as cultural changes in perception of risk to changes in availability and existence of dispensaries, to advertising, and to more biomedical considerations like potency and route of administration [5]. The strains and composition of cannabis being used and how it is being used differ dramatically from even 10–20 years ago, with substantial increases in the level of delta-9-tetrahydrocannabinol (THC) and methods of consumption that include eating, vaping, and concentrated oil extraction, the impacts of which we do not yet understand [35–39]. The full extent of how the proliferation of cannabis products may impact CUD still remains to be seen.

Discussion

At present, the epidemiology of CUD is at a somewhat shifting point in its history, with the definition of CUD, use behavior, and the cannabis itself evolving in recent years. There have been years of complementary research on biomedical aspects of cannabis and transitions from use to disorder, but the definitions of both cannabis use and CUD are evolving. There are increases in cannabis *use* among adults, but decreases among youth, and some disagreement across surveys on the direction of trends in CUD. The evolution of state cannabis laws and potentially increased availability has thus far not had the expected effect of being accessed more by youth. Whether the laws themselves are being appropriately executed, which still leave youth exposure illegal and are successfully keeping cannabis out of their hands, or if

attitudes and cultural norms have shifted such that cannabis use is less appealing to youth remains to be seen. Understanding why youth may not be using could be key in developing preventive interventions for cannabis or other drug use and other risky behaviors as well.

Even with increases in *use* among adults, the potential lack of corresponding increase in CUD is an important finding. While the neurobiological mechanisms related to cannabis use may not have changed, environmental factors such as culture, attitudes, patterns of consumption, and the product itself have changed, all of which could have implications for those mechanisms and begs the question what components of what we have learned to date are still relevant. This chapter on epidemiology of CUD has focused on survey prevalence of the occurrence of CUD, but these measurements and their evolution must be taken in context, with the understanding that biological predispositions, mechanisms, and social, cultural, economic, and geographical environments all potentially interact with each other. As any of these contributing factors changes, so does their potential impact. Therefore, the dramatic changes in the universe of cannabis cannot be discounted as scientists seek to understand CUD. Epidemiology and related disciplines should continue to compile evidence from all aspects of development to shed light on complex disorders like CUD to effectively reduce their public health burden.

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Genetic Aspects of Cannabis Use Disorder

3

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Introduction

Global rates of cannabis use are rising. According to the World Drug Report [1], nearly 182 million people have been exposed to cannabis during the last year. In most regions, the number of patients who enter treatment for cannabis use disorder (CUD) is increasing. In Africa and North America, cannabis is the main substance for which patients seek treatment. In almost all other regions, cannabis ranks second [1]. Genetics and epigenetics represent promising areas of research that could hold the keys to better screening and treatment of patients with CUD. They may also enable us to better understand the underlying pathophysiological mechanisms of the disorder.

Despite increasing numbers of patients with demands for treatment, research on CUD has lagged behind in relation to other addictive disorders for several reasons. A common assumption about the risk for CUD among users is that it is rare, based on findings from 25 years ago that relatively few cannabis users developed CUD, around 9% [2]. More recent US national data show that three out of ten regular cannabis users developed lifetime *Diagnostic and Statistical Manual for Mental Disorder (DSM)-IV* CUD. Moreover, using newer DSM-5 criteria, 19.5% of lifetime users met criteria for CUD, 23% of whom were symptomatically severe (⩾6 criteria). Of these, 48% encountered significant difficulties functioning within society (e.g., unemployment, lack of interpersonal relationships) [3]. Thus, CUD in users is not rare and can have serious consequences to the patient as well as to society.

Since most cannabis users do not develop CUD [4], it is essential to understand its etiology, which, like most addictions, is complex [4–7], involving both genetic [8] and environmental factors. Social-ecological models of alcohol use assume that in general, use is increased by factors that increase availability and desirability by normalizing use and reducing perception of harm. Other sociocultural factors may also play a role in substance use, such as in the case of certain indigenous peoples [9, 10]. Factors such as access to health care and resources (housing, employment) as well as the disintegration of traditional values may also contribute to an ecosystem that facilitates alcohol and drug abuse [11]. If these environmental factors also increase the prevalence of heavy or frequent users, then they are likely to increase the risk for CUD. Other risk factors for CUD include the age at first use, gender, trauma, as well as changing cannabis potencies (increased THC concentrations, increased THC/CBD ratios). Thus, it would be logical to integrate various environmental factors into models of genetic research.

Below is a summary of the research that has been conducted on the genetic underpinnings of CUD risk. This is followed by a discussion of what our current models lack and suggested future directions.

Heritability: Family Aggregation and Twin Studies

Since the 1980s, heritability studies have shown a tendency for drug and alcohol use behaviors to run in families. One of the first large-scale studies using data from the National Household Survey on Drug Abuse showed significant associations especially for marijuana use [12]. Meller et al. [13] further suggested a specificity in familial transmission with a greater risk of alcohol abuse in descendants of alcohol using probands. Similarly, drug use was more common among descendants of drug-using probands. Both studies showed correlations of 0.30 among parents and offspring and 0.59 between siblings. In a later study, odds ratios among 262 probands and their first-degree relatives (36 with CUD) showed an increased risk of lifetime CUD among siblings (OR = 3.6), adult offspring (OR = 6.9), and spouses

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(OR = 4.4) [14]. This study showed an association between alcohol dependence as well as antisocial personality disorders among the relatives of those with CUD. This shows that there may exist some shared genetic factors with alcohol use disorders.

Although family studies offer evidence in favor of a potential role for genetics, they cannot exclude the role of environmental factors, whether shared or unshared, in the development of substance use disorders. To further tease out these influences, several teams have assembled large numbers of families with twins and examined their cannabis and other substance use disorders. Twin studies can also compare correlations between monozygotic (MZ) and dizygotic (DZ) twins, which provides further evidence of the degree of genetic influence, as well as shared and unshared environmental factors. (For further explanations of the mathematical model, please see the article by Agrawal and Lynskey [5].)

In a meta-analysis of twin studies, Verweij et al. [15] showed overall heritability estimates between 50 and 70% for cannabis use and disorder. Two studies within their analysis showed that there was significant overlap between genetic variation in cannabis initiation and in its problematic use [16, 17]. One of the studies included data from the Netherlands twin cohort concerning the heritability of cannabis initiation [18], which reported a genetic influence of 44%, despite the more liberal attitudes in the Netherlands toward cannabis consumption versus the other cohort's nations (USA, Australia, Norway). Shared environmental factors played a significant role in cannabis initiation in this study explaining 31% of the variance. This could imply that even with recent changes in cannabis' legal status, there may be little change in the environmental impact on heritability estimates. However, the culture in the Netherlands is very different from that in the United States; and given the changing legal environment in the United States as well as other countries, it will be important to determine if genetic factors have as much of an impact on cannabis initiation, as well as CUD. Another important question is whether the rising THC concentrations and rising THC/CBD ratios will impact the influence of heritability. Most cohorts were established prior to the intensive hybridizations which led to increasing THC and decreasing CBD concentrations. Young consumers who initiate use with highly concentrated cannabis products could have a different trajectory in terms of CUD.

It would also be important to determine the potential influence of genetic variance in CUD through either a direct or an indirect pathway. Psychiatric comorbidities or cluster B personality disorders (antisocial and borderline personality disorders) have been recently shown to have an association with both cannabis use and CUD by Gillespie et al. [19].

Candidate Gene and Hypothesis-Based Studies of CUD

Some of the earliest genetic studies in CUD were based on pathophysiological hypotheses. Since then, several hypothesis-based studies have uncovered genetic variants which could contribute to the heritability of CUD. Of these genes, each contributes to less than 1% of the variance. It is possible that there are additive effects of genetic variants, as has been observed in alcohol use disorder [20]. Others have suggested that these gene candidates may simply be in genetic disequilibrium with the true causal genetic variant and that more precise techniques should be used to identify the true causal variants.

Dopamine Genes

Among the more obvious candidates for genetic vulnerability would be variability within the dopaminergic system. Numerous candidate genes have been examined to discover those that may play a role in CUD. Initial studies focused on ubiquitous regulators within the dopamine system such as catechol-O-methyltransferase (COMT) which inactivates dopamine within the brain and plays a key role in regulating mesolimbic and prefrontal cortex activity. The prefrontal cortex is responsible for cognitive, motivational, and emotional regulation. Because of its pivotal role in numerous brain processes, it has been investigated in psychosis and substance use disorders. One of the most studied polymorphisms, rs4680, results in a change from a G→A, resulting in the substitution of a valine (Val) for a methionine (Met) [21]. Both alleles are common in most of the world's populations, having an approximately 50% distribution for each. The resulting amino acid switch has been associated with changes in COMT activity. Val enzymes are associated with greater COMT activity, and Val/Val carriers have a three- to fourfold increase compared to Met/Met carriers. Heterozygotes have intermediate COMT activity [22]. Considering these observations, it was thought that cannabis users that were Val/Val carriers would have less dopamine available and a "reward deficiency syndrome" [23]. They would require greater levels of sensory stimulation to obtain adequate levels of satisfaction, and would thus be more likely to use psychoactive substances, such as cannabis, to enhance dopamine release. Several studies have examined this polymorphism with inconclusive and heterogeneous results, except in tobacco dependence. One study by Baransel et al. concluded that there was a significant association between the Val allele and cannabis dependence in a fairly small clinical sample [24]. It was not specified whether other potential confounders such as psychiatric comorbidity or other psychoactive substance use were present in their participants.

Another means by which COMT genotype could influence CUD is through early cannabis exposure. In a study by Estrada et al., they found that young psychiatric patients with a Val/Val genotype were more likely to use cannabis at an earlier age than those with another genotype [25]. This observation was not confirmed in the Avon Longitudinal Study of Parents and Children [26].

COMT may be related to certain temperamental traits such as novelty seeking. In a study of 7-month-old infants, Markant et al. [27] showed that Val/Val carriers had a greater interest in novel environmental stimuli than Met carriers, indicating that these traits may be present from a very early age. Verdejo-Garcia et al. have examined the potential influences of COMT genotype on attention and executive control [28]. In their study of cannabis users, they showed that Val/Val carriers had worse sustained attention than Val/Val non-users. Cannabis users who were also Val carriers had more difficulty shifting attention than those with the Met/Met genotype. Although *COMT* genotype did not seem to alter overall executive functioning in this study, the question remains as to the long-term cognitive evolution of cannabis users based on their COMT genotype.

In their review of the literature, Ira et al. [29] found that Val/Val carriers tend to have poorer performance in memory (n-back studies) and attention. This has been correlated with certain morphological parameters such as temporal lobe volume. None of these observations were specific to patient groups or to their specific disorders. COMT genotype may also influence other structural modifications within the brain as shown by Batalla et al. [30]. In a group of cannabis users, COMT polymorphism was associated with lesser ventral caudate and greater left amygdala volumes in cannabis users with the Val allele, whereas in non-cannabis-using controls, Val carriers had greater ventral caudate and lesser amygdala volumes. There was a modest correlation between cingulate cortex volume and lifetime cannabis use. A later study by the same group showed a nonsignificant association between long-term (>10 years) cannabis use, cumulated cannabis dose, and reduced left hippocampal volume [31]. This study also examined dopamine transporter (DAT1) tandem repeats. There was no clear relation between DAT1 polymorphisms (number of tandem repeats) and hippocampal volume in cannabis users, whereas in controls there was a clear difference, with 10/10R carriers having greater volumes. They also examined COMT and BDNF polymorphisms and showed no significant association with hippocampal volume.

Only one study that we are aware of has examined dopamine receptor polymorphisms in cannabis users. This study of 112 cannabis users versus 130 control subjects showed an increased risk of CUD in subjects with a TaqA1 allele versus the TaqA2 [32].

Another study has implicated a four-SNP ANKK1-DRD2 haplotype in cannabis use patterns among adolescents and young adults [33]. Their subjects had three types of use trajectories: (1) no cannabis use, (2) declining use, and (3) frequent use. Frequent use was associated with a family history of drug or alcohol use. They also showed that a four-SNP haplotype for the ANKK1-DRD2 was associated with cannabis use (either frequent or declining use). Their electrophysiological test (P300) was not associated with a specific genotype. These results should be replicated in other populations.

There have been other studies which have examined personality traits in cannabis users and their association with genotype. One such study showed an association between neuroticism and two proenkephalin SNPs. In this study, PENK rs2609997 (C/C, C/T), rs2576573 (A/A, A/G), and a high degree of neuroticism were associated with odds ratios of 9.2 and 8.4 of having CUD [34]. Again this was a small clinical sample (50 cannabis users and 50 cannabis dependent subjects). The study was also interesting in that they did show increased proenkephalin expression in amygdala samples with the A/G (rs2576573) versus the G/G genotype.

The family of dopamine genes are among the most widely explored genes in addictive disorders as well as psychiatric disorders. COMT may have an association with novelty seeking which could in turn encourage early experimentation with cannabis. Certain haplotypes (ANKK1-DRD2) may also have an impact on cannabis use patterns that could in turn influence the risk for CUD. The dopamine transporter gene (DAT1) may also be associated with volumes in key brain regions such as the hippocampus. The relationship to actual cognitive function remains unclear. For the moment, while these studies have often shown interesting preliminary results, it is important to confirm these in large, well-identified populations in association with eventual objective biomarkers.

Cannabinoid Genes

Another logical genetic candidate family for CUD would be genes within the cannabinoid system. A meta-analysis has shown that AAT polymorphism is associated with an increased risk of illicit substance use disorders [35]. A polymorphism (re 2023293) in the CNR1 gene, which codes for the type 1 cannabinoid receptor, may also play a role in trait impulsivity [36]. T homozygotes showed greater impulsivity and greater problems related to cannabis use.

The CNR1 may also be implicated in modifications to certain brain structures and their connections. One study has shown the presence of a G allele and both right and left hippocampal volumes in heavy cannabis users versus controls. However, the study also showed that regardless of the allele, heavy cannabis users had smaller hippocampal volumes than controls, which is in accordance with other studies [30, 31].

Other studies have shown associations between modifications in prefrontal connectivity as well as working memory and CNR1 polymorphisms. G carriers have been associated with decreased mRNA expression for CB1 receptors in the prefrontal cortex. This has also been associated with increased functional connectivity and reduced working memory [37].

Another lesser studied gene is the fatty acid amide hydrolase (FAAH). This enzyme is implicated in the regulation of endogenous cannabinoids such as anandamide. The FAAH C385A polymorphism (rs324420) has been associated with differences in FAAH activity. A positron emission tomography study has shown lower FAAH levels within the brain in A allele carriers [38]. This could mean greater CB1 receptor occupation and eventually modified cannabis consumption. Studies often examine FAAH SNPs at the same time as CNR1 SNPs. One study showed a significant interaction between CNR1 (rs2023239) genotype and withdrawal symptoms as well as a significant interaction between FAAH (rs324420) genotype and cannabis craving [39]. In a study by Tyndale et al. [40] of the same FAAH SNP, the C allele was associated with more severe withdrawal symptoms, increased positive reinforcement following cannabis use, and a significant association with CUD. Another study has also shown an association between more severe CUD and FAAH genotype [36].

Hill et al. [41] reported that the CNR1 polymorphism rs806368 A > G was associated with frequent cannabis use trajectories in young adults vs. declining use trajectories; CNR1 rs1049353 showed marginal significance with CUD. This study was performed in two populations ($n = 163$ and $n = 321$ subjects) and would require confirmation in a larger population.

In terms of hypothesis-driven studies, the genetic variations within the endocannabinoid system have shown some promise in terms of association with symptom severity, withdrawal, and craving. It would be important to replicate these studies in other populations. This genetic vulnerability may not be specific to cannabis users as it has also shown to be associated with cocaine addiction [42]. It may also play some role in the evolution of depressive symptoms in opioid users [43]. More studies are necessary to determine the role of the endocannabinoid system in substance use disorders as well as in other psychiatric disorders.

ABCB1 Transporters

ABCB1 transporters have long been studied in terms of their impact on the pharmacokinetics of various medications including chemotherapy molecules and antipsychotics. ABCB1 transporters are associated with the efflux of lipophilic molecules, including Δ9-THC. One polymorphism, rs1045642 (C3435T), has been shown to have an impact on ABCB1 kinetics with CC carriers having a more rapid efflux. One study has shown an independent association between CC genotype and CUD. The hypothesis is that faster efflux could cause more frequent cannabis consumption and thus a greater risk of CUD [35]. A later pharmacokinetic study did show some correlation between cannabinoid concentrations and ABCB1 genotype, but this has not been replicated in other studies.

Clock Genes

Clock genes are implicated in circadian rhythms. In many mental disorders, including substance use disorders, circadian rhythms are often disrupted. A classic example is the diurnal-nocturnal inversions often observed in patients with substance use disorders. In an unpublished study comparing clock genes in 94 subjects with CUD and 83 controls, there was a significant association between PER1/HES7 (*Homo sapiens* period circadian clock 1), genotype TT, and CUD. This polymorphism was also associated with early cannabis use, heavy cannabis use, and a personal history of psychiatric disorder. This association should be replicated in other larger clinical samples.

Considering the large numbers of patients who have both problematic cannabis use and sleep disorders, exploring the genetic regulation of sleep has scientific plausibility. However, current studies have been performed in relatively small clinical populations and thus need replication.

GWAS Studies

Few genome-wide association studies (GWAS) have been performed among CUD populations. The difficulty with these types of studies is assembling a large enough sample to attain statistical significance. In an initial GWAS, none of the SNPs attained statistical significance [44]. The next attempt was a meta-analysis to determine the eventual genetic basis for cannabis initiation [6]. The study failed to show any SNP that attainted statistical significance. However, their analysis revealed that only 6% of the variance in cannabis use initiation was due to common genetic factors. A subsequent study assembled the populations from three different cohorts [8]. They succeeded in finding three independent regions of the genome which included SNP associations with CUD. The possible gene candidates in these regions were a drug/metabolite transporter (SLC35G1) and a protein that may be implicated in regulating inflammation during the development of central nervous system neurons. The study is also interesting in that it showed a certain amount of overlap between certain SNPs in the CUD population and those in populations with major depressive disorder. They also found some associations with SNPs associated with schizophrenia risk. This association is in

line with many previous studies showing a heightened sensitivity to the psychotomimetic effects of cannabis in subjects with a high genetic risk for psychosis [45–47]. One final GWAS included over 32,000 subjects from various cohorts in the International Cannabis Consortium [48]. Four SNPs were identified as being significantly associated with lifetime cannabis use – one was found near the NCAM1 region, which has been associated with nicotine dependence. It is part of a gene cluster (NCAM1-TTC12-ANKK1-DRD2) that is implicated in neurogenesis and dopaminergic transmission. Other genes included CADM2, a cell adhesion molecule, and KCNT2 which encodes a potassium voltage-gated channel.

The importance of these various SNPs is still being determined. These new SNPs could eventually lead to improved hypotheses on the genesis of CUD. It would be interesting to further explore some of these SNPs with respect to their associations with certain characteristics, such as cognitive dysfunction (attention deficit, modifications in working memory, etc.) in chronic cannabis users and in other populations, such as psychotic patients. It would also be important to determine any associations with other vulnerability factors, such as age of cannabis use onset.

Whole Genome Sequencing

This is one of the more recent techniques being used to characterize and identify novel genetic markers for CUD. Gizer et al. [49] analyzed two independent cohorts: (1) a Native American cohort in which participants belonged to large multigenerational pedigrees and (2) a European ancestral cohort in which participants belonged to nuclear families. In each, participants with lifetime CUD were identified according to DSM-IV criteria. This technique then identifies low-frequency coding variants and uses enrichment analysis to evaluate associations between CUD and low-frequency variants. One new protein-coding region, *C1orf110*, was identified; little is known about this protein's function. It is however located near a gene that plays a role in cellular response to oxidative stress [50]. One regulatory region within the MEF2B gene was also identified. MEF proteins have been implicated in synapse formation and in neuroplasticity [51]. Another suggestive association was found for the PCCB gene, which has been associated with schizophrenia. Other genes that fell short of significance have been implicated in potassium ion transport channels, such as SLC24A2 and SLC24A3.

Epigenetics in CUD

If genetic studies of CUD are in their infancy, epigenetic studies are in the embryonic phase. Epigenetics examines changes to chromosomes resulting from environmental events, which do not involve modifications to DNA sequences. This can include DNA methylation, histone modifications, and non-coding RNAs. Exposure to cannabis has been linked to epigenetic modifications in animal studies [52]; and in a recent human study, significantly greater levels of DNA methylation were found in the DRD2 gene and the NCAM1 gene of cannabis users vs. controls. This may be a consequence of cannabis use or a potential marker for use [53].

Future Directions

The genetics of CUD is in its infancy. The study of genetics within psychiatric disorders has only just begun to identify some of the genes which could play a significant role in these disorders.

It is clear from research performed in family cohorts and twin studies that CUD has a strong genetic basis. Genetic heritability for CUD has been shown to be around 50–70%. Initiation of cannabis use also may have genetic influences, with a genetic variance of around 40–50%. These figures have been confirmed in several twin studies and by various teams. In contrast, the various approaches that have been used to find gene candidates that could account for more than 1% of the variance in CUD have failed. Even using GWAS techniques, the results to date have been disappointing. For example, in the study by Verweij et al. [6], their analysis showed that only 6% of the variance in cannabis initiation could be accounted for by common SNPs. Hence the question: where are all the genes hiding?

One answer may lie within the study designs used to find these genes. Since twin studies are performed on subjects who have a similar genetic background, there may be some value in pursuing rare genetic variants. This approach has shown promise in other psychiatric disorders such as psychosis. The same is true for family studies, such as that conducted by Gizer et al. [49]. While both methods may reveal some novel candidate genes, it is uncertain whether such rare gene variants would have practical implications in elucidating the pathophysiology of CUD within a more genetically varied population.

Some teams have had success in exploring subpopulations of CUD patients or in comparing their genomes with patients with other psychiatric disorders, such as major depressive disorder. Such was the case with the GWAS by Sherva et al., where they did find a 1.7% pleiotropy for genes with major depressive disorder [8].

One of the more important objectives of the DSM-5 was to facilitate identification of biomarkers that would aid the diagnosis of mental disorders. Unfortunately, this has not yet been realized, although some researchers are pursuing this avenue. In one recent study, the feasibility of using peripheral lymphocytes to quantify CB1 receptor levels [54] was

examined. While preliminary (n = 105 subjects), an association was found between peripheral CB1 receptor levels and the rs2023239 genotype. Users with a G allele had greater CB1 levels than users with only the A allele. This technique may offer some interesting insights regarding CB1 receptor regulation in cannabis users, but it will be important to determine if there is a correlation between peripheral and central CB1 receptor levels. Unfortunately, this study failed to show any differences between CB1 levels in users and nonusers and thus may not have value in terms of diagnosis or screening.

As with all scientific inquiries, the central question remains: is our current model the reflection of our current knowledge, or do we need to reconceptualize the model? Are current measurement criteria adequate? Do we need to elaborate other criteria? A majority of our existing genetic studies use a clinical system, the DSM, to identify patients with CUD. While this system may be adequate for epidemiological purposes, it may not be sufficient to enable researchers to constitute phenotypically homogenous patient groups, which might be needed to better understand the genetics of the CUD.

Addictive disorders such as CUD represent a complex phenotype. Numerous pathophysiological processes could evolve toward the full disorder. There have been many advances toward understanding the neurobiological substrates of various cognitive, emotional, and behavioral processes. In the case of cannabis initiation, there could be several observable phenomena involved, such as novelty seeking, fear of being left out, or desire to fit in with a social group. These could have distinct neurobiological substrates, such as enhanced sensitivity of the reward system and dopaminergic function in the case of novelty seeking, or altered serotoninergic and cortisol influences over social behaviors. Just as each of these "causes" of initiation would have different neurobiological substrates, their genetic basis could also be quite different. The same reasoning may hold for the various criteria associated with CUD and the progression to CUD among some, but not all, users. It is highly unlikely that there would be a single gene, or a family of genes, responsible for the interpersonal difficulties of CUD or the difficulties fulfilling professional responsibilities. Each would be the result of various neurobiological systems, with their own unique genetic and/or epigenetic basis. Inter-individual vulnerabilities could be determined according to the various individual processes implicated in these criteria.

What may be needed is a new approach to the basic aspects of psychiatric disorders, including substance use disorders. For example, a dimensional model could help us better understand these disorders and, thus, refine our hypotheses. One such initiative is the Research Domain Criteria (RDoC) project headed by the National Institute of Mental Health. This stems from the observation that current clinical diagnostic criteria are more and more at odds with our advancing knowledge from neuroimaging, genetics, and behavioral studies [55]. RDoC proposes to identify fundamental behavioral components, to determine the range of their variation (from normal to abnormal), and to develop reliable and valid measures of these fundamental components and then reintegrate these components into disorders and syndromes. From the perspective of the RDoC, we are currently examining too many variables, and possibly too many phenotypes, to obtain any clear results.

A similar dimensional approach has been undertaken for alcohol use disorder, called the Addictions Neuroclinical Assessment (ANA) [56]. One study in twins has shown that many genetic factors probably account for DSM-IV alcohol use disorder (AUD) [57]. In this model, to define alcohol use disorder, the ANA identifies three domains: incentive salience, negative emotionality, and executive functioning [56]. With the dimensional approach, each would be associated with a specific set of reproducible measurements (imaging, electrophysiology, hormonal markers, etc.) which could be compared among patients. These could enable more homogenous patient phenotypes to be established. These dimensional categories could also reveal similar traits such as novelty seeking or extreme fear in patients with different disorders. This could lead not only to an improved understanding of addictive disorders in general but also to better and more targeted behavioral or pharmacotherapy adapted to each patient's neurobiology.

Conclusion

The study of the genetics of CUD is in its very beginnings. There is a strong heritability for both initiation to cannabis use and for CUD. The search for gene candidates has shown modest promise for dopamine and cannabinoid genes. For the moment, genome-wide studies have shown a few more candidates, but they may lack sufficient power to reveal other rarer genetic variations. Other models of psychiatric disorders such as the dimensional approach may be useful for increasing study power as well as seeking more homogenous phenotypes. This could lead to a better understanding of the neurobiological processes leading to CUD as well as new and better targeted treatments.

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The Endogenous Cannabinoid System: A Cadre of Potential Therapeutic Targets

4

Steven G. Kinsey and Aron H. Lichtman

Introduction

Cannabis and its various extracts have been used for millennia [65] to treat a broad range of ailments, including depression, gastrointestinal distress, anxiety, drug dependence, and pain. Yet, scientific studies of cannabis and its component chemicals are a relatively recent development. A significant watershed moment of cannabis research occurred in the early 1960s, with the isolation and identification of two phytocannabinoids from hashish preparations (-)-trans-Δ^9-tetrahydrocannnabinol (Δ^9-THC; [31]) and cannabidiol (CBD; [74]). Whereas Δ^9-THC caused ataxia in dogs, thereby confirming its psychoactive properties [31], CBD lacked the pharmacologic properties associated with cannabis use but produced anticonvulsant properties in rodents [13, 15].

Following the identification of the primary psychoactive component of cannabis, the next major advance was the elucidation of the physiological mechanisms through which Δ^9-THC interacts with the brain and other systems. Medicinal chemistry made this second watershed achievement possible through the synthesis of synthetic cannabinoids that demonstrated structure activity relationships of cannabimimetic action [61], inhibition of adenylyl cyclase [47], and specific binding to G protein-coupled receptor [21]. Roughly a quarter of a century after the identification of THC, the first cannabinoid receptor, now known as CB_1, was cloned [70]. The second cannabinoid receptor, now known as CB_2, was cloned soon after [75].

Attention next turned to identifying the endogenous ligands that bind CB_1 and CB_2 receptors. The first identified endocannabinoid was N-arachidonoylethanolamine [22], also named anandamide from the Sanskrit word "ananda" meaning "bliss." A second endogenous cannabinoid, or endocannabinoid, was identified as 2-arachidonoylglycerol or 2-AG [72, 97]. Recent research focuses on the manipulation of multiple targets of the endocannabinoid system, including the selective activation or inhibition of the cannabinoid receptors; signaling, trafficking, and enzymatic regulation of endocannabinoids; and actions of components of the endocannabinoid system on other systems.

This chapter provides a general overview on the endogenous cannabinoid system with an emphasis of implications of pharmacological strategies targeting cannabinoid receptors or enzymes regulating endocannabinoids on cannabis use disorder (CUD).

Types of Cannabinoids

Cannabinoids are categorized based on their origin or by their structural homology with molecules known to interact with cannabinoid receptors [73]. Phytocannabinoids are plant-based cannabinoids, which include Δ^9-THC, CBD, and over a hundred structurally similar analogues present in cannabis [26]. Synthetic cannabinoids consist of hundreds of molecules based on a variety of pharmacophores that were originally developed as research tools and candidate medications but have also been subverted for illicit use and abuse [29, 107]. Endocannabinoids are naturally occurring signaling molecules that are produced and released on demand in vertebrates.

Phytocannabinoids

Phytocannabinoids are present in the cannabis plant. Some examples of phytocannabinoids are Δ^9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis [31], cannabidiol (CBD), Δ^8-tetrahydrocannabinol, and cannabinol as well as over 100 other cannabinoid molecules, many of which remain to be pharmacologically characterized.

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THC binds CB_1 [21] and CB_2 [94] receptors. Its psychoactive effects were first demonstrated in dogs [31] and later characterized in what has become known as the "Billy Martin tetrad" assay, a commonly used battery of four in vivo tests used to detect cannabinoid effects in rats and mice. The tetrad response includes catalepsy (i.e., rigid posture as assessed in ring immobility or bar tests), decreases in locomotor activity, analgesia (i.e., decreases in nociceptive behavior as assessed in the tail-flick test), and decreased body temperature [67]. In particular, preclinical [108, 109] and clinical [40] studies provide empirical evidence supporting the effectiveness of cannabinoid-based drugs in ameliorating cannabis withdrawal symptoms.

Growing attention has been drawn to CBD largely because of its recent successes as an add-on therapy in reducing seizures in Lennox-Gastaut syndrome [99] and Dravet [23] patients. Indeed, small studies and case reports have long suggested a beneficial role of CBD in treating epilepsy [20, 81]. CBD has also long been found to produce anticonvulsant effects in rodents [12, 14, 15] and more recently was shown to reduce seizures in a mouse model of Dravet syndrome through a likely GPR55 mechanism of action [51]. Additionally, CBD produces anti-inflammatory [62, 66] and antinociceptive effects [53, 60, 106] in preclinical mouse studies. Emerging research is beginning to assess CBD in preclinical models of drug abuse [59]. Cannabidiol does not bind either cannabinoid receptor and likely exerts any physiological effects through multiple mechanisms, including 5HT1A, adenosine reuptake, and GPR55 [59]. Cannabidiol has also been proposed to negatively modulate CB_1 activity by binding to a yet unknown allosteric site on the CB_1 receptor [56]. Although the efficacy of CBD in CUD remains to be systematically evaluated, the cannabis-derived medication nabiximols (containing approximately equal amounts of THC and CBD) shows some promise in reducing cannabis craving and a subset of withdrawal signs in cannabis-dependent individuals [100–102].

Synthetic Cannabinoids

Synthetic cannabinoids are laboratory-produced compounds that bind to cannabinoid receptors to activate (i.e., agonism), block (i.e., neutral antagonism), or actively inhibit (i.e., inverse agonism) the target receptor. Selective CB_1 or CB_2 receptor antagonists/inverse agonists are powerful experimental tools for determining whether an observed effect occurs through either or both receptors. Examples of CB_1 receptor antagonists include rimonabant [87] and AM251 [33]. Commonly used CB_2 selective receptor antagonists include AM630 [81] and SR144528 [88].

Synthetic cannabinoid agonists were initially synthesized as research tools but have gained recent notoriety after being sold as quasi-legal "incense" products (e.g., Spice, K-2, Buzz) that are smoked [68]. The effects and safety profile of most synthetic cannabinoids are largely unknown because they were not developed for human consumption. JWH-018 is one of the first synthetic cannabinoid agonists that was found in these incense products. JWH-018 has a higher affinity than THC for CB_1 and has greater efficacy in activating CB receptors [9], which may help explain the unusual psychogenic effects of "spice" products in people. Two exceptions to the synthetic cannabinoids marketed for recreational use are dronabinol and nabilone, which are synthetic THC analogues that have FDA approval for the treatment of chronic wasting [90]. Notably, nabilone significantly reduced marijuana relapse as well as irritability and disruptions in sleep and food consumption in daily, nontreatment-seeking marijuana smokers undergoing abstinence [39].

A strategy to harness the anti-inflammatory effects of the endocannabinoid system while avoiding the psychoactive effects is to develop CB_2 receptor-selective agonists. Some examples of CB_2-selective agonists include HU-308 [42], AM1241 [49], and O-3223 [54]. These compounds have anti-inflammatory effects in rodents but do not cause behavioral changes at moderate doses.

Endocannabinoids

The third category of cannabinoids is endogenous cannabinoids (i.e., endocannabinoids), which are cannabinoid receptor agonists that are internally produced in vertebrates. The two broadly accepted endocannabinoids are anandamide [22] and 2-AG [72, 97], both of which bind to and activate either cannabinoid receptor. Other lipids that bind to cannabinoid receptors at high concentrations in cell culture, but may have limited effects in animals, include noladin ether [41]; N-arachidonoylethanolamine [48]; O-arachidonoylethanolamine, also known as virodhamine [84]; and hemopressin, a peptide-derived purported endocannabinoid [37]. The endocannabinoids possess short half-lives because of their rapid hydrolysis. Thus, considerable attention has been dedicated to elucidating their enzymatic pathways, as well as developing inhibitors of endocannabinoid-regulating enzymes as research tools and for proof-of-principle as potential medications.

Endocannabinoid Metabolism

Endocannabinoids are synthesized on demand from lipid precursors in the cell membrane [2] and are tightly regulated by enzymes that control their synthesis and hydroly-

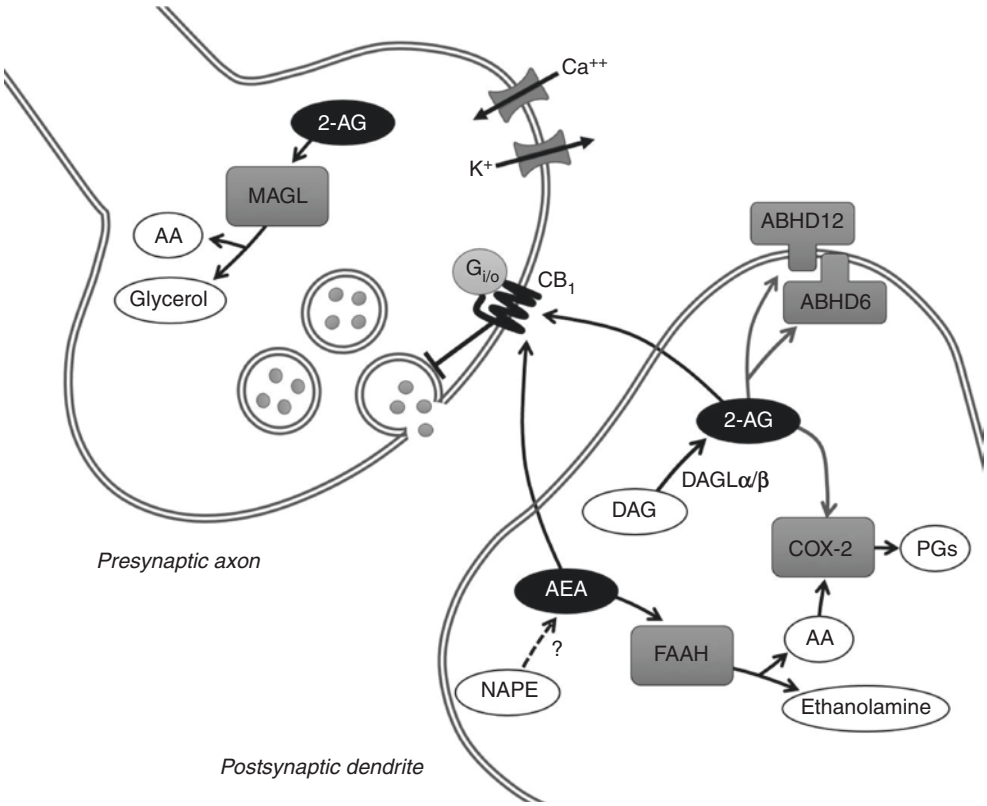

Fig. 4.1 Simplified schematic of endocannabinoid metabolism and retrograde signaling

sis (Fig. 4.1). Although multiple biosynthetic pathways have been proposed for anandamide production [6], its hydrolysis by fatty acid amide hydrolase (FAAH) into ethanolamine and arachidonic acid has been firmly established [16, 17]. The synthesis of 2-AG is better established than that of anandamide and is synthesized from diacylglycerols by the enzymes diacylglycerol lipase α and β [5, 30, 98]. 2-AG is degraded primarily by the catabolic enzyme monoacylglycerol lipase (MAGL) into glycerol and arachidonic acid [24].

Exogenous administration of anandamide or 2-AG produces minimal pharmacological effects in animals, because of their rapid degradation by FAAH or MAGL, respectively [6]. However, pharmacological inhibition of FAAH increases tissue levels of anandamide as well as other fatty acid amides [1]. FAAH inhibition or genetic deletion of FAAH typically has analgesic and anxiolytic effects, especially in tests that incorporate a stress component ([25]; cf. [11]). Notably, a study using FAAH (−/−) mice demonstrated that repeated administration of anandamide leads to a substantially reduced magnitude of CB_1 receptor downregulation and desensitization, as well as rimonabant precipitated-withdrawal signs, than repeated administration of an equally effective dose of Δ^9-THC [27]. These findings bolster the argument that FAAH inhibitors not only elicit minimal acute cannabimimetic pharmacological effects but also CB_1 expression and function are retained following prolonged FAAH inhibition.

Similarly, MAGL inhibition, for example, with JZL184, increases tissue levels of 2-AG throughout the body [64]. Alterations in endocannabinoid levels affect a broad range of physiological and behavioral systems. Multiple labs have provided evidence that FAAH or MAGL inhibition produces a range of effects including analgesia [25, 83] and decreases in anxiety-like behaviors [78].

The physiological effects of FAAH and MAGL are not limited to endocannabinoids. For example, FAAH also hydrolyzes other fatty acids including oleamide, which promotes sleep [19], and N-palmitoylethanolamine (PEA) [18] which binds to peroxisome proliferator receptor-α (PPAR-α) receptors and has anti-inflammatory effects (Lo [105]). Similarly, the ability of MAGL to catabolize 2-AG into glycerol and arachidonic acid makes it an important contributor to free arachidonic acid in the brain, liver, and lung, but not in the gut [76]. Arachidonic acid is a critical precursor to many bioactive molecules such as prostaglandins; thus inhibiting or upregulating MAGL may have broad ranging physiological effects that are independent of cannabinoid receptors. For example, the MAGL inhibitor JZL184 attenuates neuroinflammation by limiting the availability of arachidonic acid [76].

A consequence of stimulating the endocannabinoid system is to ameliorate withdrawal signs in preclinical models of cannabinoid, opioid, and nicotine dependence. Thus, the endocannabinoid system offers multiple potential drugga-

ble targets for reducing symptoms associated with cannabis use disorder. Indeed, the MAGL inhibitor JZL184 and the FAAH inhibitor URB597 reduce paw tremors induced by THC withdrawal in mice [92]. Whereas CB_1 receptor expression and function are preserved in FAAH (−/−) mice [27] or wild-type mice treated repeatedly with FAAH inhibitors [93], prolonged high-dose JZL184 can mimic some of the same effects of chronic THC administration, leading to tolerance and dependence [93]. It is noteworthy that, at such high doses, JZL184 inhibits both MAGL and FAAH [64] and that tolerance does not develop following repeated administration of low doses of JZL184 that partially inhibit MAGL and do not elevate brain anandamide levels [55]. Similarly, dual FAAH-MAGL inhibitors elicit a full constellation of pharmacological effects in the tetrad assay, whereas inhibition of either enzyme alone produces a subset of effects in this assay [63]. Thus, inhibiting either MAGL or FAAH appears to differ from inhibiting both MAGL and FAAH.

Although FAAH and MAGL represent the major respective hydrolytic enzymes of anandamide and 2-AG, other enzymes also contribute to the degradation of these ligands. For example, approximately 15% of 2-AG is catabolized by α-β hydrolase 6 (ABHD6) and ABHD12 [7]. ABHD6 and ABHD12 are bound to the intracellular and extracellular side of the cell membrane, respectively, whereas MAGL is unbound in the cytosol, and thus the three enzymes appear to regulate different pools of 2-AG [7]. Similarly, cyclooxygenase-2 (COX-2) degrades anandamide [111] as well as 2-AG [44] and produces bioactive metabolites [34].

Cannabinoid Receptors

Both endocannabinoids primarily bind to the two cannabinoid receptor subtypes, CB_1 and CB_2, and anandamide also interacts with other receptors, including transient receptor potential cation channel subfamily V member 1 [115] and the peroxisome proliferator-activated receptor binding domain [8]. CB_1 is heterogeneously distributed throughout the central and peripheral nervous systems [36, 43]. In the neuron, activation of CB_1 inhibits adenylyl cyclase and K^+ and CA^{++} channels and stimulates MAP kinase [34]. Cannabinoid receptors represent the most highly expressed G protein-coupled receptors in the nervous system [43], acting through $G_{i/o}$ protein signaling pathways. Thus, it is not surprising that the endocannabinoid system modulates so many physiological and behavioral processes.

CB_1 receptors are predominantly expressed on presynaptic neurons throughout the nervous system. These receptors are highly expressed in brain regions such as the hippocampus, amygdala, nucleus accumbens, substantia nigra, and cerebellum [103], as well as in the spinal cord [28], in the dorsal root ganglia [46], and at lower levels in non-neural peripheral tissues. Unlike the mu opioid receptor, brainstem regions controlling vegetative function are devoid of CB_1 [43], which is consistent with the lack of overdose deaths associated with cannabis. CB_1 mediates most of the psychoactive effects of cannabinoids including processing of reward, stress responses, pain, cognition, and motor control. Genetic deletion of CB_1 prevents the well-characterized psychogenic effects of cannabinoids [58, 114]. Given the broad expression of CB_1, its functions vary by the cell populations in which it is expressed, as well as which ligands are presented. For example, CB_1 is expressed on both glutamatergic (i.e., excitatory interneurons) and GABAergic (i.e., inhibitory interneurons) presynaptic neurons. Accordingly, CB_1 stimulation leads to the inhibition of neurotransmitter release, and the localized action may be inhibitory or disinhibitory depending on the given neural circuit.

CB_2 receptors are primarily expressed on cells of the immune system, including macrophages, microglia, lymphoid, and mast cells [10]. CB_2 is also sparsely expressed in nerves and neurons following injury [113], as well as in healthy brainstem [95], and may also contribute to some behavioral aspects of endocannabinoid function, such as modulating emotionality [32] as well as reward and stimulant addiction [112]. Thus, although CB_2 is generally considered to have immunomodulatory effects, it may also have subtle but important behavioral effects. However, its low expression in the CNS and the lack of selective CB_2 antibodies present substantial challenges in investigating its function on neurons.

Recently, multiple compounds have been developed that bind to allosteric sites on CB_1, resulting in positive or negative allosteric modulation of CB_1 activity [52, 85, 110]. Allosteric binding of a ligand is believed to change the confirmation of orthosteric binding sites, which are considered the active binding site, leading to increased or decreased binding of the orthosteric agonist. Common examples of allosteric modulators are benzodiazepines and ethyl alcohol. Examples of CB_1-positive allosteric modulators include lipoxin A [77], ZCZ011 [50], and GAT211 [57, 96]; negative allosteric modulators include pepcan-12 [4], cannabidiol [56], pregnenolone [104], and ABD1075 [38]. Initial studies indicate that the structurally related CB_1-positive allosteric

modulators ZCZ011 and GAT211 elicit CB_1-depedent analgesic effects in mice that do not undergo tolerance following repeated administration but lack pharmacological activity when administered alone in the tetrad assay [50, 96]. Additionally, mice given repeated administration of GAT211 show no evidence of physical dependence [96]. Whereas the CB_1-positive allosteric modulators ZCZ011 and GAT211 show, in vivo, evidence for CB_1, in vivo activity of other allosteric modulators is unclear. Further preclinical research is needed to determine whether CB_1-positive allosteric modulators possess potential for reducing CUD.

The endocannabinoid system modulates brain circuits related to learning, stress, reward, and anxiety-related brain circuits. In addition to euphoria, two of the primary acute psychoactive effects of cannabinoid administration in humans are decreased anxiety and depression. Perhaps not surprisingly, chronic cannabis users report increased anxiety or depression during abstinence, which can lead to relapse of drug use [3, 82]. CB_1 is expressed throughout the mesolimbic reward pathways and influences dopamine and opioid signaling, which accounts for the rewarding effects of cannabis use and may also contribute to withdrawal symptoms [65]. Other systems that may contribute to the addictive properties of cannabinoids include serotonin, acetylcholine, steroid hormones, adenosine, and stress-related hormone systems including catecholamines and corticotrophin-releasing hormone [65]. Given the broad expression of CB_1 in the brain, it is perhaps not surprising that repeated activation of the cannabinoid receptor has downstream effects on multiple neurotransmitters and circuits.

Endocannabinoid modulation of the stress response has also been implicated in cannabinoid dependence. For example, rats repeatedly administered with the synthetic cannabinoid agonist HU-210 and then subjected to withdrawal had elevated corticotrophin hormone levels and activity in the amygdala [91], a region that is critically involved in emotional regulation. Thus, activation of CB_1 has been proposed as a functional anti-stress response system [69]. For example, blocking CB_1 activity reverses the blunted corticosterone release that can result from chronic stress [79]. In mice, CB_1 activation decreases restraint stress-induced corticosterone release, but CB_1 blockade induces adrenocorticotropic hormone release, indicating that CB_1 regulates the stress response [86]. Endocannabinoid signaling also contributes to the suppression of the neuroendocrine stress response by inhibiting GABAergic transmission [45]. Activation of CB_1 on GABAergic neurons inhibits the release of GABA, which disinhibits the neuronal circuit and activates medial prefrontal cortex projection neurons, which indirectly inhibit the release of corticosterone [45].

Inhibiting endocannabinoid catabolic enzymes blunts stress-induced corticosterone release but varies by the enzyme manipulated. MAGL inhibition, but not FAAH inhibition, blunts restraint-induced corticosterone release in mice [89]. Psychological stress also increases CB_1 expression in the rat ventromedial prefrontal cortex [71], further supporting the idea that endocannabinoids modulate the stress response. Thus, altered CB_1 function may directly contribute to cannabinoid withdrawal symptoms and may also indirectly increase stress, a well-known risk factor for drug relapse.

Conclusion

Although cannabinoids have been used for millennia for their medicinal properties [73], the scientific investigation of these fascinating signaling molecules has rapidly developed over the past few decades. Given the general public acceptance of "medical" cannabis and the fact that cannabis remains the most highly used illicit drug over the past 40 years, the perception that cannabis is a safe drug devoid of significant side effects is not surprising. Following much preclinical and clinical research demonstrating the existence of a cannabis dependence, cannabis withdrawal syndrome and cannabis use disorder were added to the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* [3]. These syndromes are characterized by sleep disturbances, increased anxiety and depression, and drug cravings. Thus, increases in cannabis consumption for intended medicinal use, as well as continued recreational use of this drug, come with an inherent risk of an increased prevalence and incidence of CUD, as well as a need for effective treatments.

Despite the plethora of basic knowledge gained from the flurry of research activity throughout the past few decades on the endocannabinoid system, the FDA has approved only two cannabinoid-based medications. Notably, each of these drugs, Marinol and Cesamet, reduced cannabis withdrawal symptoms. Nonetheless, the endocannabinoid system offers many potential therapeutic targets for the treatment of CUD and other disorders. Specific strategies include cannabinoid receptor agonists, CB_1 receptor-positive allosteric modulators, and inhibitors of endocannabinoid hydrolytic enzymes (e.g., FAAH and MAGL). The availability of safe drugs targeting the various components of the endogenous cannabinoid system may provide new treatments for CUD. In addition, understanding the genetic contribution of CUD (e.g., see [35]) may also contribute to reducing the occurrence of CUD as well as treatments through personalized medicine (Table 4.1).

Table 4.1 Glossary of common cannabinoid terms

2-Arachidonoylglycerol (2-AG): An endogenous cannabinoid that activates both CB_1 and CB_2 receptors
ABHD: α-β hydrolase. ABHD6 and ABHD12 catabolize approximately 15% of 2-AG into arachidonic acid and glycerol. Both are membrane bound, with ABHD6 on the intracellular side and ABHD12 on the extracellular side
Anandamide (AEA, N-arachidonoylethanolamine): An endogenous cannabinoid that activates both CB_1 and CB_2 receptors
CB_1 (CB1R): Cannabinoid receptor subtype 1. Expressed at high levels in neural tissue. Activation of CB_1 results in euphoria and other psychoactive effects of cannabinoids including THC
CB_2 (CB2R): Cannabinoid receptor subtype 2. Expressed at high levels in immune cells and at low levels in the brainstem. Activation of CB_2 is typically anti-inflammatory
Cannabidiol (CBD): A bioactive phytocannabinoid that does not bind CB_1 or CB_2 receptor
Cyclooxygenase (COX): Enzymes that synthesize arachidonic acid into prostaglandins and other physiologically active signaling molecules. The COX-2 subtype can degrade anandamide
Dronabinol: Synthetically produced THC. Marketed in the USA as Marinol
Endocannabinoid: Endogenously produced cannabinoid receptor agonists, including anandamide and 2-AG, and possibly others, that bind to and activate cannabinoid receptors
Fatty acid amide hydrolase (FAAH): A serine hydrolase that degrades anandamide and other N-acylethanolamines as well as N-acyl taurines
G protein-coupled receptor (GPCR): A subtype of metabotropic receptors that are bound to G proteins. Binding of the receptor activates guanosine triphosphate (GTP) proteins, which act as second messengers to activate ion channels. Cannabinoid receptors are the most abundant GPRC in the brain
JZL184: A highly selective MAGL inhibitor, thereby increasing tissues levels of the endocannabinoid 2-AG. Also inhibits FAAH at high doses
Monoacylglycerol lipase (MAGL): Primary enzyme responsible for catabolizing the endocannabinoid 2-AG into arachidonic acid and glycerol. Inhibition of MAGL elevates 2-AG levels by preventing 2-AG degradation but also decreases free arachidonic acid levels. Thus, MAGL is also a gatekeeper of free arachidonic acid
Nabilone: A synthetic THC analog. Marketed in the USA under the name Cesamet
Peroxisome proliferator receptor (PPAR): A nuclear receptor protein that is bound by various fatty acids, including N-palmitoylethanolamine (PEA) and anandamide. FAAH inhibition may activate PPAR-α receptors by increasing the availability of both PEA and anandamide
PF-3845: Highly selective FAAH inhibitor. Shown in increase anandamide levels in the brain and other tissues
Phytocannabinoid: Cannabinoid produced by cannabis plant
Rimonabant (SR141716A): CB_1 receptor-selective antagonist with inverse agonist properties. Commonly used tool to probe the involvement of CB_1 in physiological processes. Marketed in Europe as Accomplia
SR144528: CB_2 receptor-selective antagonist with inverse agonist properties. Commonly used tool to probe the involvement of CB_2 in physiological processes
(-)-Trans-Δ^9-tetrahydrocannabinol (THC): Phytocannabinoid with physiological activity. The primary psychoactive component of cannabis, responsible for the well-characterized "high" and other behavioral effects of cannabis
Transient receptor potential (TRP): Ion channel. TRPV1 is expressed on nociceptors and responsible for the painful effects of capsaicin, found in hot peppers. Anandamide is also a ligand for TRPV1

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Cannabidiol and Cannabis Use Disorder

5

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Epidemiological, Social, Economic, and Health Impact of Cannabis Use Disorders

Cannabis, such as hashish or marijuana, is the most commonly used illicit drug worldwide. Available data suggest that the prevalence and incidence of its consumption will keep rising over the next years, representing a serious public health problem [1]. Approximately 24% of patients initiating treatment for substance abuse present a diagnosis of cannabis use disorder (CUD) [2]. According to the last World Drug Report [3], approximately 183 million people used marijuana (cannabis) in 2015. In addition, in North America, the largest cannabis herb market, prevalence of cannabis consumption rates has followed an upward trend in the United States where 42% of persons over age 12 used cannabis at least once in their lifetime, 11.5% used within the past year, and 1.8% met diagnostic criteria for cannabis abuse or dependence within the past year [4–7].

CUD encompassing intoxication, withdrawal, and dependence criteria accounted for two million of disability-adjusted life years (DALYs) globally, with the United States among the countries with higher age-standardized DALY rates [5]. Importantly, CUD also increases the probability of developing additional drug and alcohol use disorders [8], cognitive impairment, as well as schizopsychotic symptoms [8–11]. Moreover, several studies point out the problematic association between the use of marijuana among young people and lower income, greater need for socioeconomic assistance, unemployment, criminal behavior, and lower satisfaction with life, representing a tremendous social and economic impact [12–16]. In addition, cannabis consumption in United States has been linked with impaired driving and accidents, including fatal accidents [17].

Therapeutic Management of CUD

One-half of the patients in treatment for CUD reported symptoms of withdrawal. Although not medically serious, cannabis withdrawal should be a focus of treatment because it may serve as negative reinforcement for relapse to cannabis use in individuals trying to abstain [18]. Despite these data, there are no medications approved by either the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) for the treatment of CUD. However, many studies have been carried out to find out new pharmacotherapies, and these fall into to two main approaches: (1) attenuate symptoms of cannabis withdrawal and (2) reduce the subjective and reinforcing effects of cannabis.

To date, some clinical trials evaluated the therapeutic usefulness of different pharmacological approaches for the management of cannabis withdrawal and the modulation of the reinforcing effects of and craving for cannabis [2]:

1) *Cannabinoid CB1 receptor agonist substitution*: synthetic Δ^9-tetrahydrocannabinol (THC, dronabinol), legally marketed in the United States as Marinol®, demonstrated to be efficacious in some human laboratory studies for reducing cannabis withdrawal symptoms [19–22].

2) *Lithium*: a mood stabilizer that showed some efficacy in two small open-label clinical studies [23, 24]. However, a recent randomized placebo-controlled trial did not demonstrate any therapeutic effect [25].

3) *Neuromodulation of brain circuits mediating withdrawal symptoms*: a wide range of drugs such as divalproex, bupropion, nefazodone, or lofexidine (among others) were tested with inconclusive results [26–28]. Additionally, similar pharmacological strategies were proposed to reduce the

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reinforcing effects and craving for cannabis through activation of the cannabinoid receptor or the modulation of other neurotransmitter systems [2, 29].

It is important to consider that the efficacy of pharmacological treatments for cannabis dependence, as with other substance use disorders, may require additional psychosocial interventions to maintain a high level of motivation in the patient for cannabis cessation. Among these psychotherapeutic strategies, *motivational enhancement therapy (MET)*, *cognitive behavioral therapy (CBT)*, *contingency management (CM)*, *supportive-expressive psychotherapy (SEP)*, and *family and systems interventions* [2, 29] have the strongest evidence base.

However, the overall clinical outcome among those who received treatment in randomized trials is poor, and long-term abstinence is achieved by <20% of the patients [30]. The limited knowledge of the neurochemical mechanisms underlying CUD may contribute, at least in part, to the low efficacy of the medications evaluated to date. Therefore, it is necessary to invest effort and resources in identifying new drugs that, alone or in combination, may improve the efficacy of the treatment of CUD.

Rationale or Justification for Testing the Efficacy of Cannabidiol in CUD

Cannabis sativa contains hundreds of chemical entities produced by secondary metabolism including cannabinoids, terpenes, and phenolic compounds, each with potential interesting biological properties [31]. To date, over 120 cannabinoids, oxygen-containing C21 aromatic hydrocarbons, have been isolated from the plant [32].

Delta-9-tetrahydrocannabinol (Δ^9-THC), well known for its psychoactive effects, is the main component of *Cannabis sativa* and the first cannabinoid to be discovered and studied. Isolated for the first time by Gaoni and Mechoulam in 1964 [33], Δ^9-THC mediates the rewarding properties of cannabis through binding to specific G-protein-coupled receptors, mainly the cannabinoid CB_1 receptor [34].

Other major phytocannabinoids isolated from the plant are *cannabidiol (CBD)*, *cannabichromene (CBC)*, *cannabigerol (CBG)*, *cannabidivarin (CBDV)*, and *tetrahydrocannabivarin (THCV)* [35].

CBD, one of the main compounds, together with Δ^9-THC, present in the plant *Cannabis sativa*, was isolated by Mechoulam and Shvo in 1963 [36]. Since then, a variety of research groups studied its effects in basic and clinical studies. The results obtained suggest that CBD may have beneficial effects for the management of neurological disorders such as epilepsy [37–39], multiple sclerosis [40, 41], and Parkinson's [42, 43] or Alzheimer's disease [44, 45]. Moreover, there is a growing body of evidence suggesting that CBD improves cognition [46] and neurogenesis [47, 48] and may have antipsychotic [49–54], anxiolytic [55–58], and antidepressant-like effects [59–61].

Antipsychotic-Like Effects of CBD

Several studies evaluated the potential of CBD as an antipsychotic in genetic and pharmacological animal models [46, 49, 51, 62, 63]. First studies revealed that pretreatment with CBD improved prepulse inhibition deficits in the dizocilpine (MK-801) model in C57BL6JArc mice [51]. Similar results were observed after chronic administration of CBD [64]. Also, CBD improved prepulse inhibition (PPI) disruption in spontaneously hypertensive rats (SHR) [65] and in male Swiss mice exposed to amphetamine [66], two well-accepted models of schizophrenia-like phenotypes.

Furthermore, CBD improves additional core symptoms present in schizophrenic patients, such as impaired social interaction and cognitive deficits. In mice exposed to acute and chronic treatment with the NMDA receptor antagonist MK-801 [67–69], as well as in the *neuregulin 1* mutant mice (*Nrg1* TM HET) [70], CBD improved social interaction deficits. Interestingly, CBD significantly reversed the cognitive impairment induced by MK-801 in mice [69]. Recently, Osborne and colleagues showed that chronic administration of CBD restored working memory and improved social interaction in a neurodevelopmental model of schizophrenia-like phenotypes (prenatal poly I:C infection) [71]. However, in other studies, CBD failed to reverse cognitive impairments and positive or negative symptoms [68, 72]. These discrepancies may be due to the strain of mice/rat employed, the doses of CBD tested, and the experimental conditions used.

In line with these preclinical findings, clinical studies suggest that CBD may be effective, safe, and well tolerated for the treatment of psychosis in patients. CBD improved psychotic symptoms in patients with Parkinson's disease [43]. In 2012, a clinical trial demonstrated that CBD improved the positive and the negative symptoms of schizophrenia in a similar way to the antipsychotic drug amisulpride [50]. CBD did not alter the secretion of prolactin nor induce weight gain or extrapyramidal symptoms, commonly side effects of current antipsychotics [50, 73].

Taken together these results indicate that CBD may be of interest as an antipsychotic drug. Additional studies, including preclinical and large-scale clinical trials, are needed to further explore the efficacy and safety of CBD as an antipsychotic.

Anxiolytic-Like Effects of CBD

Converging human and rodent studies revealed that CBD displayed anxiolytic-like effects [55, 74]. In the rat Vogel

conflict test, a widely used animal model of anxiety, CBD showed anxiolytic effects like benzodiazepines [57]. In agreement with these results, Resstel and colleagues demonstrated that CBD displayed anxiolytic-like effects, similar to the benzodiazepine diazepam, in a contextual conditioned fear paradigm in rats [58]. Also, CBD showed anxiolytic-like effects in a model of posttraumatic stress disorder [75] and in the elevated plus maze test [76] in rats. Chronic administration of CBD in pre-limbic prefrontal cortex reduced freezing in rats subjected to a fear conditioning paradigm [76, 77]. In C57BL/6Arc mice, chronic administration of low doses of CBD induced moderate anxiolytic-like effects [78]. However, other studies failed to show an anxiolytic-like effect of CBD at higher doses [57, 79, 80], suggesting a possible bell-shaped dose-response curve for CBD's anxiolytic effects, with positive actions noted at moderate but not high doses [56, 81].

Complementary human studies revealed that CBD produced anxiolytic actions in healthy volunteers exposed to an experimental paradigm for inducing anxiety [82, 83]. Also, CBD reduced anxiety and psychotic-like symptoms induced by Δ^9-THC [83]. Indeed, CBD reduced anxiety in social phobic [84] and posttraumatic stress disorder [85].

In conclusion, these results support a role of CBD as a new anxiolytic drug for the treatment of multiple anxiety-related disorders.

Antidepressant-Like Effects of CBD

Several studies suggest that CBD displays antidepressant-like effects in rodent models. In the forced swim test, the administration of CBD produced antidepressant-like effects [61, 86]. Similar effects were obtained by Sartim and colleagues, using microinjections of CBD in the medial prefrontal cortex [59]. In the olfactory bulbectomy mouse model of depression (OBX), CBD reversed the OBX-induced hyperactivity and anhedonia [60]. Similarly, using a genetic animal model of depression, the Wistar-Kyoto (WKY) rat, CBD improved performance on a novel object recognition test and reduced anhedonia by increasing saccharine preference [87].

In summary, these results demonstrated that CBD might be of interest for the treatment of depressive disorders and support the need for further animal and clinical studies to clarify its potential therapeutic value.

Neuroprotective Properties of CBD

CBD shows neuroprotective properties following different insults in animal models involving neurodegeneration, mainly due to its antioxidant [88, 89], antiapoptotic [90, 91], and anti-inflammatory properties [92–94]. In a rat model of Parkinson's disease, CBD provided neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons [89, 95]. Also, CBD had potent and long-lasting neuroprotective effect when administered pre- or post-ischemia [96–98]. Furthermore, CBD displayed neuroprotective effects against hypoxia-ischemia [90, 99–101], striatal lesions induced by 3-nitropropionic acid [102] and iron [103], and arterial ischemic stroke [104] in newborn rats, mice, and piglets.

Research to characterize the mechanisms underpinning these neuroprotective effects indicates that CBD reduced glutamate release, stabilized the mitochondrial membrane, reduced apoptotic activation, improved cell proliferation and dendritic density, reduced glial activation, increased adenosine levels, and prevented NF-KB activation [90, 96, 105–109]. Despite these interesting data, further studies are needed to clarify its mechanism of action and its potential therapeutic use in different neurological and psychiatric diseases involving neurodegeneration.

Neurochemical Mechanisms Underlying CBD Effects

The mode of action of CBD is still not fully understood. More than 65 different targets, including voltage-gated sodium channel-1 (VGSC-1), voltage-gated calcium channels (VGCC) (CaV3X), cannabinoid receptors (CB_1r, CB_2r), G-protein-coupled receptor 55 (GPR55r), vanilloid receptor 1 (TRPV1), serotoninergic receptor 1A (5-HT_{1A}), μ and δ opioid receptors, and peroxisome proliferator-activated receptor (PPARγ), have been described as direct or indirect targets of CBD [75, 110–115].

Russo and colleagues demonstrated that CBD acts as an agonist at the 5-HT_{1A} receptor [111]. Other results suggested that activation of the 5-HT_{1A} receptor may partially explain the anxiolytic [75, 84, 116, 117], antidepressant [59, 60], and antipsychotic-like effects [62, 118] and the neuroprotective properties [119, 120] displayed by CBD.

Furthermore, other studies suggest that CBD behaves as an antagonist of CB_1r/CB_2r at very low doses [113]. However, a recent study revealed that CBD might act as a negative allosteric modulator of the CB_1r [121]. Also, CBD can act as a CB_2r inverse agonist, a fact that may explain, at least in part, its known anti-inflammatory actions, modulating different components of the immune response [122–124]. In support of this, the selective CB_2r antagonist SR144528 prevented the CBD-induced blockade of chemotaxis of macrophages [123].

In addition, CBD may be an allosteric modulator of ligand binding to mu opioid receptors, closely related to addictive processes [114].

Future research will be required to identify the pharmacological relevance of each of these molecular targets for CBD's myriad effects.

CBD Lacks Potential as a Drug of Abuse

Some controversy regarding its potential as a drug of abuse significantly hampers the development of further basic and clinical studies. In many European countries, CBD is not under any special restriction. In fact, CBD is present in nabiximols (marketed as Sativex®) currently approved for the treatment of spasticity in multiple sclerosis. In contrast, in the United States, CBD is currently classified as Schedule 1 under the Controlled Substance Act (CSA), meaning it has high potential for abuse with no accepted medical benefit. This is because CBD is a component of the cannabis plant [125], which is also Schedule 1. Furthermore, CBD is classified as a Schedule 2 drug according to the Controlled Drugs and Substances Act in Canada [126]. Despite these conflicting regulatory approaches, to our knowledge no previous studies were specifically designed to evaluate the potential properties of CBD as a drug of abuse.

However, in contrast to THC, some studies show that CBD does not induce euphoria or intoxication [127–129]. This lack of psychoactive activity appears to be related to its low affinity for CB_1r (100-fold less than THC) [130]. Interestingly, recent studies carried out in mice in our laboratory further demonstrate that CBD does not behave like other addictive substances [131]. A range of doses were evaluated in different assays commonly used to assess the reinforcing and motivational properties of drugs. CBD did not produce conditioned place preference (CPP) at any of the doses tested (15, 30, or 60 mg/kg, i.p.) in this well-established paradigm to detect the reinforcing properties of drugs [132–135]. These results are in agreement with previous studies of CPP in rats [136, 137].

CBD also did not induce a withdrawal syndrome 12 h after the abrupt cessation of chronic administration (30 mg/kg, i.p., 6 days, twice a day). Withdrawal was measured using locomotor activity alterations, and somatic signs (rearings, groomings, or rubbings), which were not detected.

We also evaluated whether CBD was self-administered orally, a model that provides the most direct point-to-point test of addictive behavior [138]. CBD failed to induce oral self-administration—it did not increase the number of active lever presses, nor the consumption of drug during a fixed ratio 1 schedule (FR1; i.e., reinforcement delivered after each response), compared to the water control group.

Taken together, these results suggest that CBD lacks properties of an addictive substance. Indeed, to date, no significant adverse effects were observed in any of the preclinical or clinical studies carried out with CBD. Comparable human abuse liability studies will need to determine whether CBD lacks addictive potential or, if not, could be rescheduled to facilitate basic and clinical studies to elucidate CBD's potential therapeutic use for the treatment of neuropsychiatric diseases.

CBD and Drug Use Disorders

The pharmacological properties of CBD (anxiolytic, antidepressant, antipsychotic, and neuroprotective actions) and its apparent lack of addictive potential suggest that CBD may be of interest for the treatment of drug use disorders.

Some pioneer animal studies revealed that CBD reduced reward-facilitating effect and withdrawal signs associated with morphine [139, 140]. Also, CBD reduced heroin craving and relapse and normalized the mesolimbic alterations of CB_1r and AMPA glutamatergic R1 receptors [141]. Interestingly, CBD reduced the seizures induced by cocaine [142] and the conditioned place preference induced by cocaine or amphetamines [137]. Transdermal CBD administration also reduced context-induced and stress-induced cocaine and alcohol seeking in rats. Interestingly, CBD was able to avoid relapse during 5 months after its last administration, whereas plasma and brain CBD levels remained detectable only for 3 days [143]. Interestingly, our group demonstrated that CBD reduced ethanol consumption, the motivation to drink, and relapse for ethanol in mice [138]. Indeed, CBD attenuated the neurodegeneration induced by a binge-drinking model of alcohol in mice [47].

CBD and Cannabis Use Disorders

Regarding CUD, some previous studies suggest that CBD may be useful for its clinical management. CBD reduced some negative effects induced by Δ^9-THC such as anxiety [83], cognitive impairments, psychotic-like symptoms [144], and alterations in emotional processing [145]. In patients taking cannabis for medicinal purposes, a more balanced CBD/THC ratio concentration might improve therapeutic end points by minimizing the THC side effects [146, 147].

A previous clinical trial studied 134 cannabis users on two different days (a week apart): one day without cannabis and one day intoxicated with their own chosen cannabis [148, 149]. A sample of cannabis (as well as saliva) was collected from each user and analyzed. Because of highest and lowest CBD content of cannabis, two groups of individuals were directly compared (n = 22 each). Despite the marked impairment in prose recall of individuals smoking cannabis low in CBD, participants smoking cannabis high in CBD showed no memory impairment [149]. Indeed, to evaluate the impact of CBD on the reinforcing effects of THC on

addictive behavior, the implicit "wanting" and the explicit "liking" of cannabis were analyzed on 94 cannabis users [148]. Greater attentional bias to drug and food stimuli was found in the low CBD/THC ratio group on the intoxicated day (implicit "wanting"). Moreover, the high CBD/THC ratio group was associated with lower ratings of pleasantness for drug stimuli (explicit "liking"), while no group difference was detected in craving or stoned ratings [149].

Cannabinoid replacement therapy [150] could be a useful approach for the management of CUD. Initially, synthetic THC or similar compounds were examined, such as dronabinol (Marinol) or nabilone (Cesamet). Subsequently, the ~50/50% combination of THC with CBD in an oral mucosal spray (nabiximols or Sativex in United States or EU, respectively) showed some interesting therapeutic benefits pointing out CBD-mediated attenuating effects on THC intoxication, psychotic symptoms, and other adverse psychological effects. In addition, CBD may contribute to reductions in anxiety and cognitive impairment associated with illicit cannabis use.

A recent double-blind placebo-controlled randomized clinical trial demonstrated that a 6-day inpatient regimen of nabiximols suppressed cannabis withdrawal symptoms during inpatient abstinence and achieved successful retention in treatment longer than placebo. Despite the successful control of cannabis withdrawal, there were high rates of relapse to cannabis following discharge from the unit (69% at 1 month) in both groups [151]. This result was consistent with the lack of long-term abstinence achieved by any medication-assisted withdrawal without ongoing psychosocial and/or clinical support.

Trigo et al. evaluated the tolerability of high or self-titrated Sativex dosages for 8 weeks in a non-treatment-seeking population with CUD. This study was double-blind, placebo-controlled and measured effects in "smoke as usual" or cannabis abstinence conditions. The results revealed that high fixed Sativex doses reduced cannabis withdrawal symptoms during abstinence without modifying craving [75]. Subsequently, the effect of Sativex (self-titrated) in combination with motivational enhancement and cognitive behavioral therapy was evaluated in five treatment-seeking subjects diagnosed with CUD, during a 3-month open-label clinical trial with a 3-month follow-up. The results indicated that the combination of Sativex and psychotherapy progressively reduced the amount of cannabis use, craving, and withdrawal scores [152, 153].

The evidence supporting the therapeutic usefulness of the combination of THC and CBD for CUD is modest; however, there is a need for clinical trials evaluating long-lasting effects with a higher number of patients. Consequently, two follow-up studies examining longer-term (12 weeks) outpatient cannabis relapse prevention using nabiximols were recently performed (Australian Government National Health and Medical Research Council grant #1088902, Centre for Addiction and Mental Health, and National Institute on Drug Abuse) [150, 153]. Results from the latter study revealed that nabiximols, in combination with MET/CBT, was able to reduce cannabis use and was well tolerated. Additional studies using higher doses of nabiximols are still needed to determine the therapeutic potential for cannabis use disorder.

However, there may still be a concern about whether the presence of THC in nabiximols could be problematic, especially in the still unexplored long-term treatment of CUD. For this reason, recent attention has been paid to the potential clinical efficacy of CBD alone. To date, only a few case reports have evaluated the therapeutic usefulness of CBD alone for CUD. Crippa et al. [154] administered CBD for 11 days (300 mg on day 1, 600 mg on days 2–10, and 300 mg on day 11) to a 19-year-old female with cannabis dependence who experiences withdrawal symptoms when she tried to cease cannabis use. Daily assessments showed a rapid decrease in withdrawal symptoms, leading to a score of zero in all tests by day 6. A 6-month follow-up showed a relapse to cannabis use, but at a lower frequency (once or twice a week vs. 7 days a week). Another case report [155] evaluated the use of a CBD oil in a 27-year-old male presenting with a long-standing diagnosis of bipolar disorder and addiction to marijuana (including daily use). After initiating treatment with CBD oil, the patient reported a decrease in anxiety and sleep disturbances, as well as a complete cessation of marijuana use. Recently, a clinical study analyzed the effect of oral CBD during 8 days of cannabis self-administration on the subjective effects and cannabis ratings in non-treatment-seeking healthy cannabis smokers. No differences were found in comparison with placebo-treated participants [156]. This may be due to the short period of CBD treatment, the experimental design (using non-treatment-seeking participants), or the poor bioavailability of oral CBD.

Several clinical trials are now under way to evaluate the effects of CBD alone on CUD (McLean Hospital, NCT03102918), cannabis dependence (University College London, NCT02044809), cannabis withdrawal (the University of New South Wales, NCT02083874), or smoked marijuana's (5.6% THC) subjective, reinforcing, cognitive, and cardiovascular effects (National Institute on Drug Abuse (NIDA), NCT01844687). While the data are too preliminary and not consistent, there is increasing interest in determining whether CBD monotherapy could be useful for CUD management, particularly since it could present a nonintoxicating approach to medical management of CUD symptoms.

Our laboratory has recently conducted a series of studies in mice [157] to analyze the effects of CBD on the spontaneous withdrawal syndrome developed after 7 days of treatment with CP-55,940 (a 45-fold more potent CB1 agonist compared to THC) [158]. Motor activity, withdrawal signs, and anxiety-like behavior were studied in abstinent C57BL6/J

male mice treated with CBD or its corresponding vehicle (VEH). In addition, gene expression analyses were performed to examine possible neurochemical correlates. CBD at the highest dose administered (20 mg/kg) significantly reduced the increased motor activity induced by spontaneous cannabinoid withdrawal (Fig. 5.1a). All doses of CBD (5, 10, and 20 mg/kg) blocked the increase in the number of rearings (Fig. 5.1b) and dose-dependently reduced the increase in the number of rubbings (Fig. 5.1d) and jumping (Fig. 5.1e). Also, the number of grooming episodes was reduced during cannabinoid withdrawal as described elsewhere [159], and CBD showed a significant tendency toward a normalization effect (Fig. 5.1c). All the doses of CBD tested abolished the high levels of anxiety-like behaviors induced by cannabinoid withdrawal (Fig. 5.2a). Thus, administration of CBD improved the most prominent symptoms of CP-55,940-induced spontaneous cannabinoid withdrawal. While promising, the much higher potency of CP-55,940 compared to THC suggests caution in interpretation of the generalizability of these results.

Gene expression studies revealed that CBD dose-dependently reduced the CB_1r upregulation in the nucleus accumbens (NAc) induced by spontaneous cannabinoid withdrawal (Fig. 5.2c). These results are in agreement with our previous work showing that CBD reduced ethanol consumption, at least in part, through the reduction of CB_1r gene expression in the NAc of C57BL/6 J mice [138]. Previous studies also suggest that CBD acts as a noncompetitive allosteric modulator of CB_1r modifying anandamide hydrolysis by inhibiting its catabolic enzyme, the fatty acid amide hydrolase [110, 121]. Thus, it is tempting to speculate that modification of endocannabinoid levels may be closely related to the neurochemical changes and possibly the behavioral effects induced by CBD.

In conclusion, these results provide unequivocal evidence about the efficacy of CBD to reduce the behavioral disturbances associated with the cannabinoid-induced spontaneous cannabinoid withdrawal in mice. Furthermore, the gene expression analyses of CB_1r, closely involved in the cannabinoid-related reinforcing actions, provide relevant information about the neurochemical processes involved in the regulation of cannabinoid withdrawal by CBD. Despite this novel information, further preclinical studies are needed to evaluate the potential therapeutic actions of CBD in the management of CUD and elucidate the precise underlying neurobiological mechanisms. This research also suggests targeting the cannabinoid withdrawal syndrome due to its close association with relapse and the multiple behaviors that CBD could modify in relation to withdrawal.

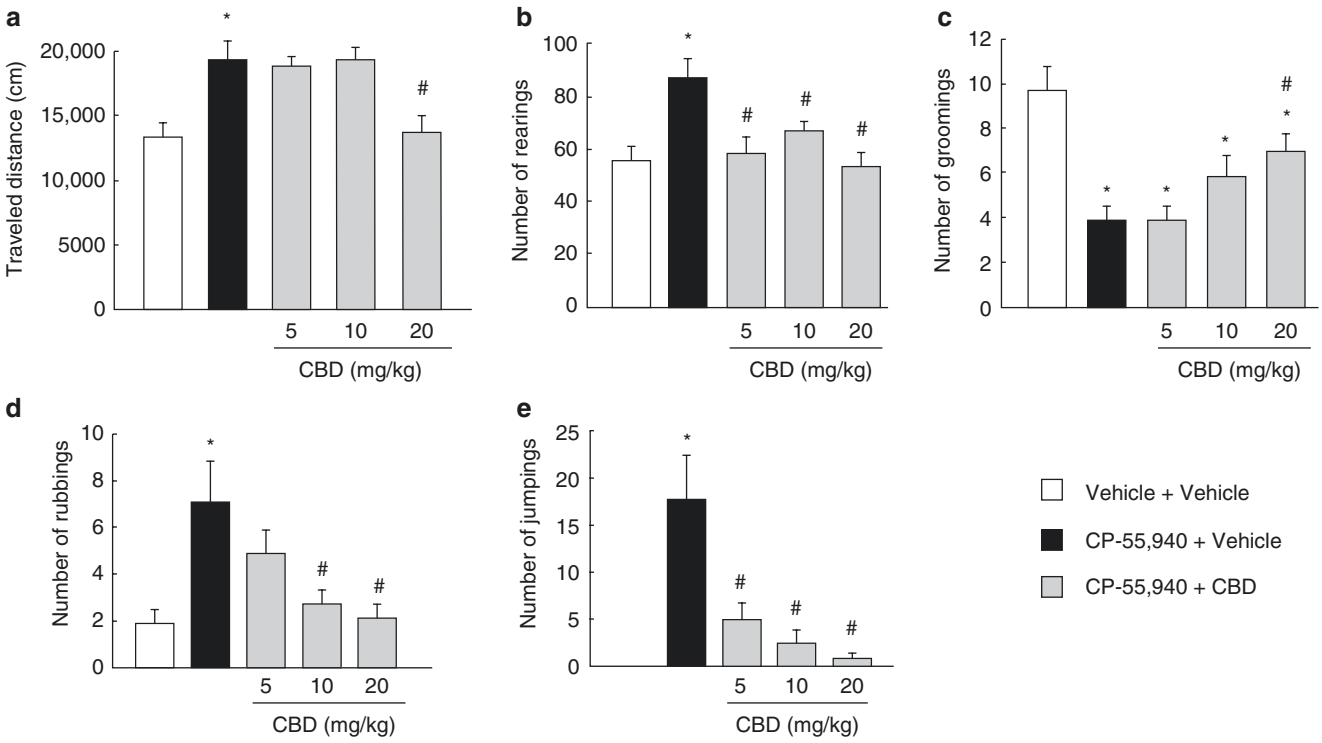

Fig. 5.1 Assessment of spontaneous cannabinoid withdrawal and CBD actions on motor activity and behavioral signs of abstinence (number of rearings, groomings, rubbings, and jumping). Columns represent the means and vertical lines ±SEM of traveled distance (cm) by mice in the open-field test and the number of rearings, groomings, rubbings, and jumping. *, values from CP-55,940-treated mice that are significantly different ($p < 0.05$) from vehicle + vehicle-treated mice. #, values from mice treated with CP-55,940 + CBD that are significantly different ($p < 0.05$) from CP-55,940 + vehicle-treated mice (one-way ANOVA followed by the Student-Newman-Keuls test)

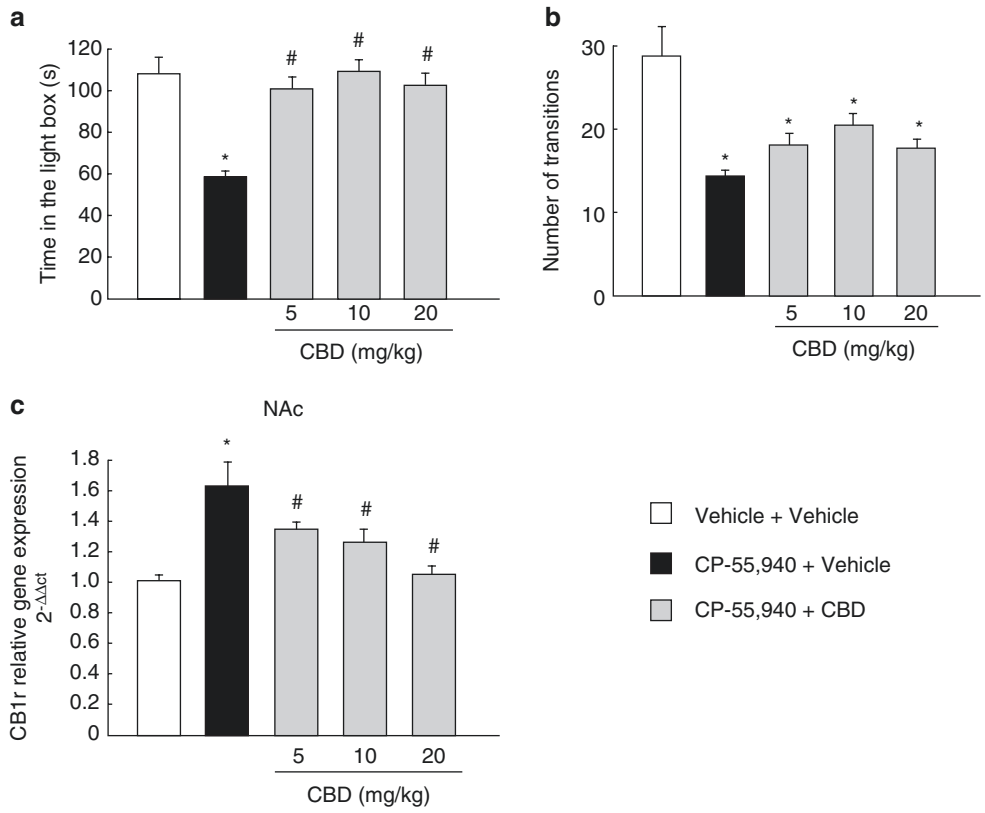

Fig. 5.2 Panels 2**a**–**b**: Assessment of anxiety-like behavior related with spontaneous cannabinoid withdrawal and its subsequent treatment with CBD. Panel A shows the evaluation of the time in the light box, and panel B shows the evaluation of the number of transitions. Columns represent the means and vertical lines ±SEM of time (s) in the light side and number of transitions. Panel 2**c**: Gene expression alterations of CB1r in the NAc induced by spontaneous cannabinoid withdrawal and subsequent CBD treatment. Columns represent the means and vertical lines ±SEM of 2-ΔΔCt. *, values from CP-55,940-treated mice that are significantly different ($p < 0.05$) from vehicle-treated mice. #, values from CP-55,940 + CBD-treated mice that are significantly different ($p < 0.05$) from CP-55.940 + vehicle-treated mice (one-way ANOVA followed by the Student-Newman-Keuls test)

Conclusions and Future Directions

CBD is a promising drug for the treatment of different neuropsychiatric and drug use disorders based on its pharmacological profile (anxiolytic, antidepressant, antipsychotic, and neuroprotective properties), its lack of intoxicating properties, and apparent lack of serious adverse consequences (although these have not been well studied in long-term trials). Focusing on CUD, the available data obtained from animal and human studies suggest that CBD may attenuate or abolish some of the clinical symptoms associated with cannabis withdrawal, which could help individuals maintain abstinence. However, these promising results should be further studied in basic models and in long-term clinical trials with sufficient numbers of patients to determine the usefulness of CBD in the pharmacological management of CUD.

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6 The Molecular Basis of Cannabinoid Activity: Application to Therapeutics Design and Discovery for Cannabis Use Disorders

David R. Janero, V. Kiran Vemuri, and Alexandros Makriyannis

Introduction

Molecular Basis of Cannabinoid Activity

Preparations derived from *Cannabis* sp. (e.g., "marijuana," dried cannabis leaves, flowers, stems, and seeds; "hashish," derived from the resin of the plant's flowers) have been used for recreational and medicinal purposes since antiquity. In the 1930s and 1940s, laboratory neuropharmacological investigations documented the central excitatory activity of crude cannabis extracts. By 1970, advances in the separation sciences and biophysical methods of chemical analysis enabled the isolation and definitive structure determination of several plant cannabinoids from the over 100 phytocannabinoids and related chemical constituents now known to be present in cannabis, most prominently Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (Fig. 6.1) [1]. Identification of Δ^9-THC as the main psychoactive constituent of cannabis focused considerable experimental and clinical attention on this phytocannabinoid, especially regarding the molecular basis of cannabis' physiological effects in the central nervous system (CNS) and the reasons for the stereospecificity of THC action [2–5]. In 1988, the first evidence of a high-affinity, stereoselective cannabinoid G protein-coupled receptor (GPCR) in brain, subsequently termed cannabinoid receptor 1 (CB1R), was published [6]. Notwithstanding its activity at peroxisome proliferator-activated receptors (PPARs) and GPR55 receptors [7], Δ^9-THC's activation of central CB1Rs is considered critical for manifestation of its psychoactive effects *in vivo* [8].

Cloning, expression, and imaging of brain CB1R provided strong impetus to search for additional cannabinoid GPCRs and for endogenous cannabinoids (endocannabinoids) that engage and activate them. By the mid-1990s, these lines of experimental inquiry resulted in several breakthroughs: cloning and expression of a second cannabinoid GPCR, named cannabinoid receptor 2 (CB2R); discovery and structure determination of two major endocannabinoid lipid transmitters derived from arachidonic acid, arachidonoylethanolamine (anandamide; AEA) and 2-arachidonoylglycerol (2-AG), that can activate CB1R and CB2R as orthosteric agonists (Fig. 6.1); and identification of various enzymes involved in AEA and 2-AG biosynthesis and biotransformation [2–5]. Of the latter, the most well-studied are the serine hydrolases fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL) that terminate the signaling functions of, respectively, AEA or 2-AG [9, 10]. Collectively, the cannabinoid receptors, their endocannabinoid ligands, and the enzymes responsible for establishing endocannabinoid tone through the interplay of biosynthesis and biotransformation comprise the endocannabinoid system, one of the most important mammalian signaling networks that itself may interact with others to produce unique biological effects [2, 3, 11]. Although the principal, most intensively studied components of the endocannabinoid system are summarized diagrammatically in Fig. 6.2, long-chain amide and ester fatty-acid derivatives other than AEA and 2-AG have been identified that may act (in)directly with CB1R and/or CB2R, constituting a family of bioactive lipids, the endocannabinoid metabolome [12, 13]. Likewise, other 2-AG hydrolases including ABHD6 and ABHD12 help MGL regulate specific endocannabinoid signaling pathways *in vivo* [14, 15] (Fig. 6.2).

Largely because of the historically well-recognized ability of cannabis – and, particularly, its key phytocannabinoid ingredient, Δ^9-THC – to elicit psychobehavioral responses for both recreational pleasure and therapeutic benefit, much attention has been focused on endocannabinoid system neurobiology. In mammals, CB1R is the most abundant brain GPCR and is localized to presynaptic neurons, whereas AEA and 2-AG are synthesized in the postsynaptic neuron from endogenous membrane lipids in response to various (patho) physiological stimuli and are released therefrom and trans-

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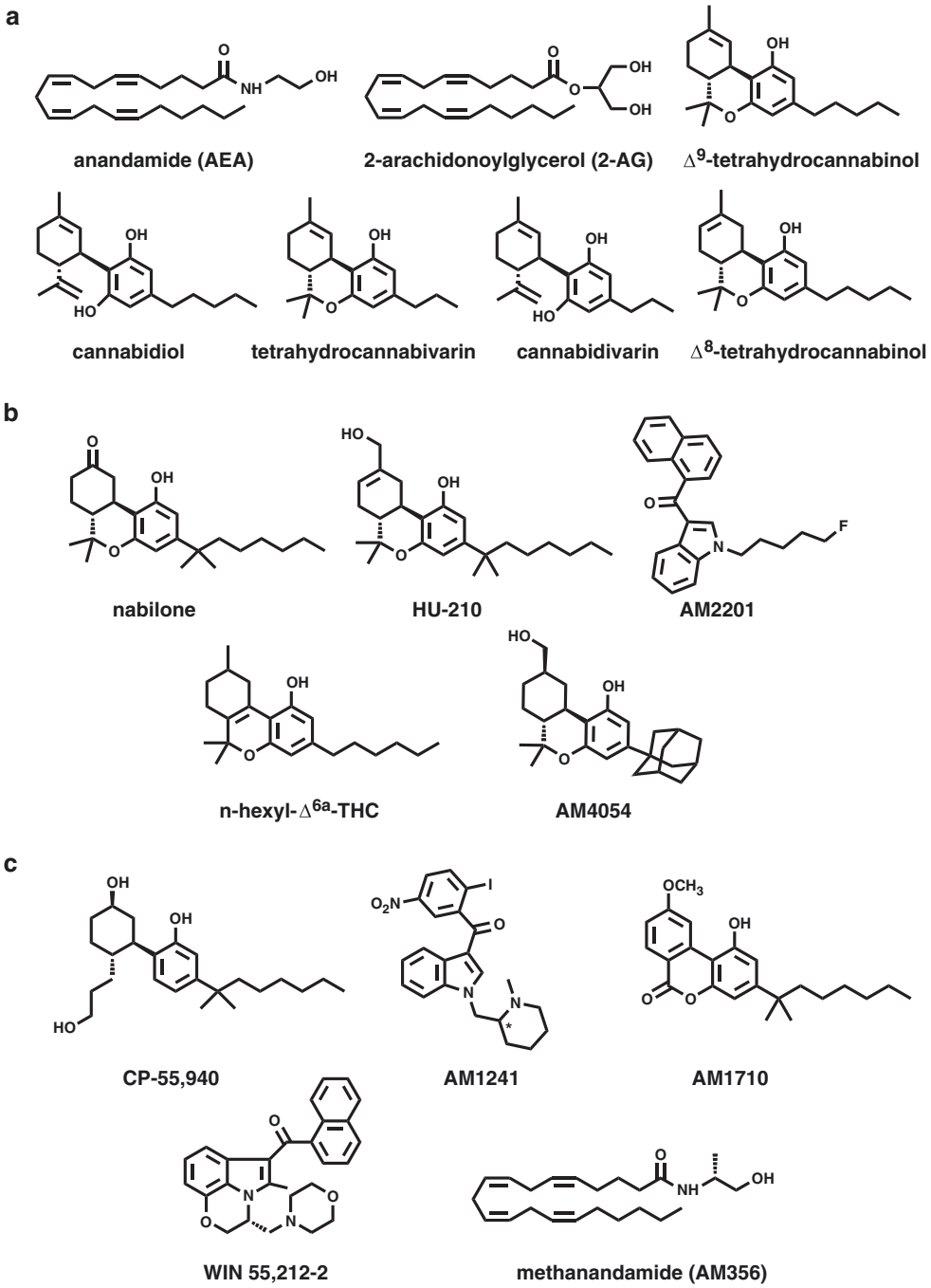

Fig. 6.1 Structures of principal cannabinergic ligands discussed in the text, grouped into their distinct families. (**a**) Endo- and phytocannabinoids; (**b**) CB1R/CB2R agonists; (**c**) cannabinoid agonist pharmacological tools; (**d**) CB2R agonists; (**e**) CB1R antagonists/inverse agonists; (**f**) CB1R antagonist/inverse agonist imaging agent; (**g**) CB1R periphero-neutral antagonist; (**h**) CB2R antagonist/inverse agonist; (**i**) FAAH and AEA transport inhibitors

ported across the synaptic junction by a yet ill-defined carrier mechanism [16] (Fig. 6.2). This compartmentalization and the on-demand nature of AEA and 2-AG production endow endocannabinoid signaling in the CNS with hallmark characteristics of retrograde directionality and relatively brief duration of action distinct from typical neurotransmitters that are stored in active form within secretory vesicles and released in quanta from the presynaptic compartment to engage target postsynaptic receptors [16]. Retrograde signal transmission via CB1R in the CNS controls various motor, cognitive, emotional, and sensory functions to influence pain perception, hormonal activity, thermoregulation, and cardiovascular, gastrointestinal, and respiratory physiology [17]. Activation of central CB1R mediates most of the psychotro-

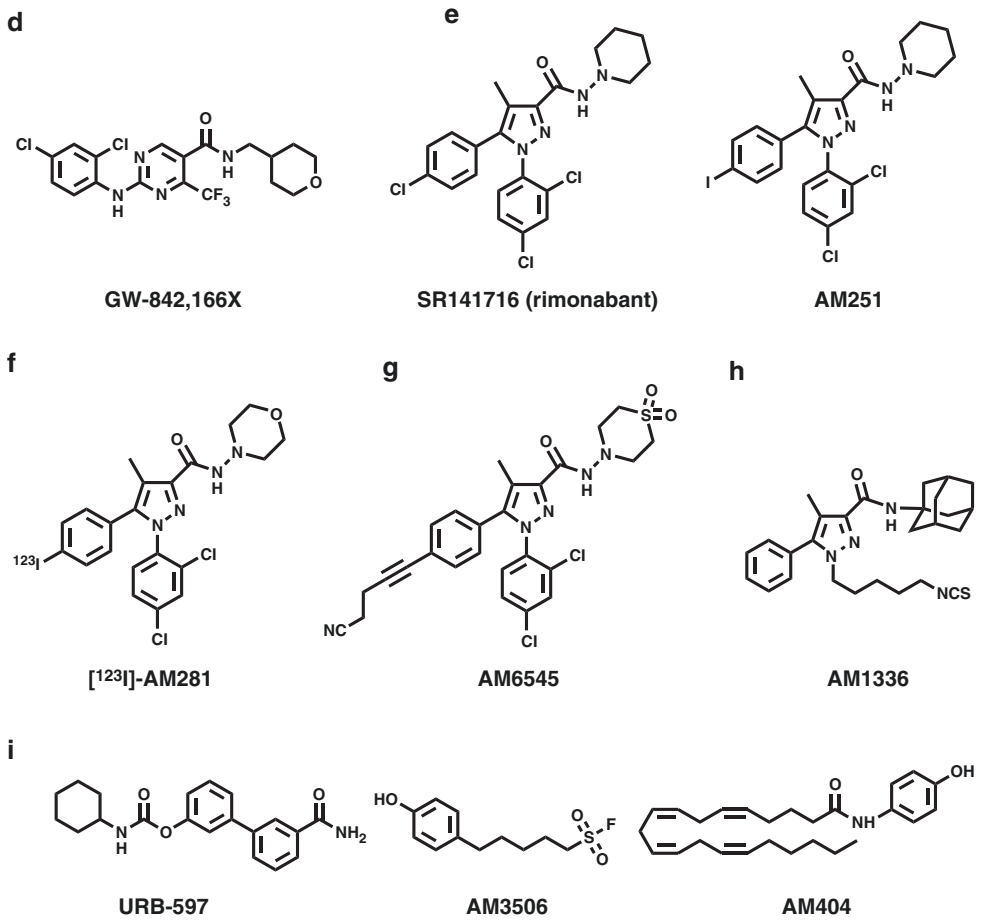

Fig. 6.1 (continued)

pic and behavioral effects of cannabis [8]. CB1R is also expressed in peripheral tissues, especially in those (e.g., adipose, liver, endocrine pancreas) responsible for energy balance and substrate metabolism/storage [7]. CB1Rs at peripheral sites help regulate fundamental physiological and metabolic processes such as energy storage and expenditure, fat deposition, and reproduction [18, 19]. Detectable at very low basal levels in the healthy CNS and to a greater degree in the diseased/injured brain, under homeostatic conditions, CB2R is expressed mainly in the periphery by immunocompetent and hematopoietic cells, osteoclasts, and osteoblasts and mediates immune responses, inflammation, inflammatory and neuropathic pain, and bone remodeling [7]. Canonical CB1R and CB2R coupling through inhibitory G proteins ($G_{i/o}$) inhibits adenylyl cyclase (i.e., cellular cyclic AMP formation) and certain ion channels and activates select protein kinases [20].

Pharmacologically, the receptor-dependent nature of classical endocannabinoid signaling via CB1R and CB2R and the central role of rapid catalytic endocannabinoid inactivation by FAAH and MGL in regulating tissue AEA and 2-AG tone and signaling intensity have helped make these four proteins prime targets for drug discovery efforts aimed at therapeutic endocannabinoid-system modulation [2, 21–25]. As discussed below, modalities employed for developing cannabinoid receptor-targeted medications through rational small-molecule ligand design include CB1R and CB2R orthosteric agonists and antagonists and active-site FAAH and MGL inhibitors.

Cannabinoid Therapeutics Design and Discovery

CB1R Agonists

The main psychotropic plant cannabinoids in cannabis are Δ^9-THC and, to a lesser extent, Δ^8-THC, Δ^9-tetrtahydrocannabivarin, and other natural phytocannabinoids including the nonpsychotropic (−)-cannabidiol (CBD) and cannabidivarin (Fig. 6.1) [26]. Pharmacologically, Δ^9-THC is a CB1R partial agonist with moderate affinity for CB1R and CB2R, whereas Δ^9-tetrtahydrocannabivarin has been reported to be a weak CB1R antagonist and a modest CB2R agonist. The precise molecular mechanism by which CBD acts remains undefined, although cannabidivarin and

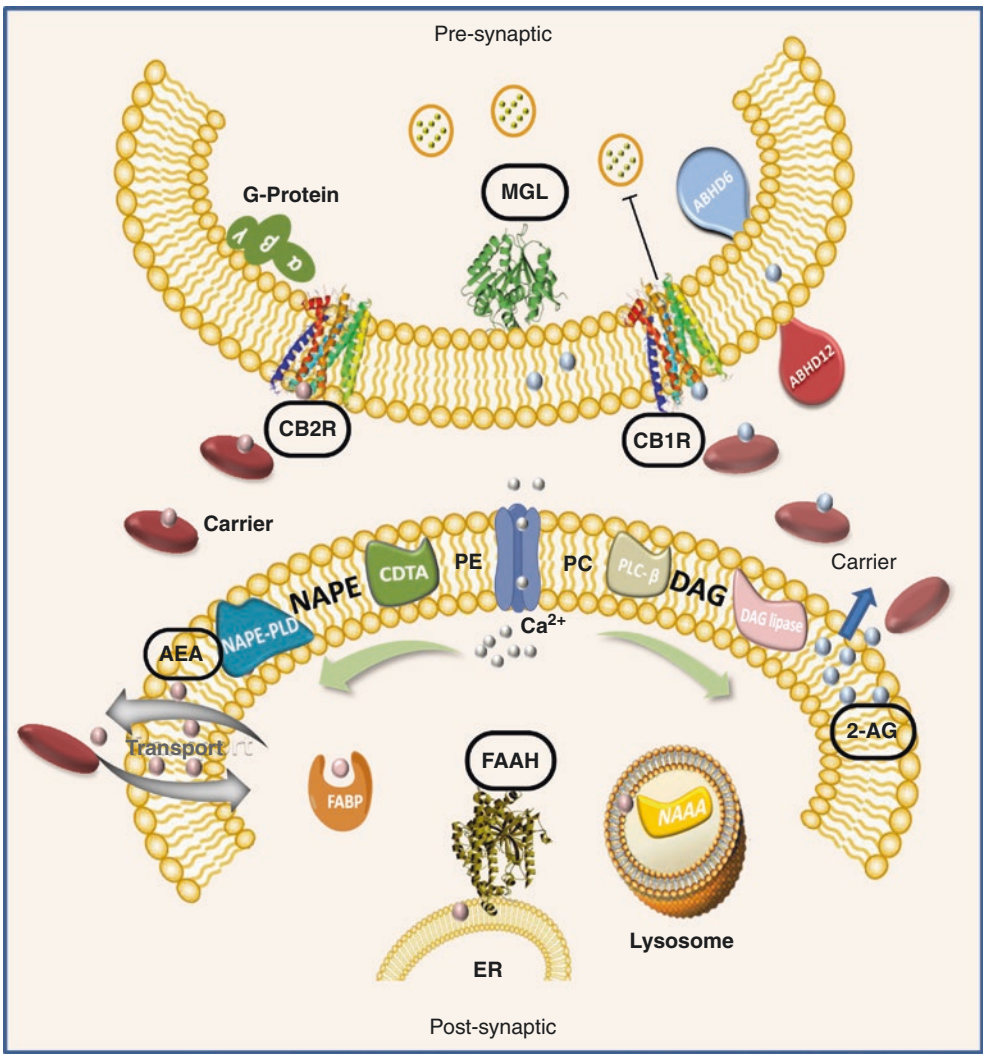

Fig. 6.2 Molecular basis of cannabinoid activity in the central nervous system. The termini of a pre- and postsynaptic neuron are depicted diagrammatically at the synaptic junction. The six components of the endocannabinoid signaling system most extensively discussed in the text are labeled in boxed bold type and abbreviated as follows: AEA anandamide (arachidonoylethanolamide), 2-AG 2-arachidonoylglycerol, CB1R cannabinoid receptor 1, CB2R cannabinoid receptor 2, FAAH fatty acid amide hydrolase, MGL monoacylglycerol lipase. For completeness, other cellular and endocannabinoid-system components are also included, as abbreviated: ABHD6 α-β hydrolase domain-containing protein 6, ABHD12 α-β hydrolase domain-containing protein 12, DGL diacylglycerol lipase, ER endoplasmic reticulum, FAPB fatty acid binding protein, NAPE N-arachidonoylphosphatidylethanolamine, PC phospholipase C, PD phospholipase D, PE phosphatidylethanolamine

CBD display low affinities for CB1R and CB2R [2, 27]. These CB1R agonists have been evaluated in human studies as potential treatments for varied indications including anorexia, emesis, spasticity, neuropathic and cancer-related pain, epilepsy, and dyslipidemias [28].

Although a few clinical trials with CB1R orthosteric agonists are still ongoing, publicly disseminated efficacy data are lacking, and it is unknown whether the trial results would ever support marketing cannabis-based therapeutics free of undesirable neurobehavioral issues due to central CB1R activation. Despite the long-standing dominance of target-based drug discovery, identification of all four prime endocannabinoid-system therapeutic targets (CB1R, CB2R, FAAH, and MGL) over 20 years ago, continued target profiling, and the plethora of synthetic ligands for these targets designed, synthesized, and tested *in vitro* and *in vivo* for potential preclinical therapeutic efficacy, only two such ligands – both CB1R agonists – have reached market status. The Δ^9-THC analog nabilone (Cesamet®) (Fig. 6.1) is classified under the US Controlled Substance Act by the US Drug Enforcement Administration (DEA) as a Schedule-II drug approved to treat chemotherapy-induced nausea/eme-

sis, and synthetic Δ^9-THC itself (dronabinol, Marinol®) has gained regulatory approval as a DEA Schedule-III drug for treating anorexia associated with weight loss in AIDS patients [29, 30]. A cannabis extract-based combination of Δ^9-THC and CBD in a 1:1 ratio administered as a buccal spray (nabiximols, Sativex®) has been approved in the United Kingdom to treat multiple sclerosis-related spasticity and pain in advanced cancer patients [31]. Most recently, a pharmaceutical formulation of purified CBD (Epidiolex®) was granted orphan drug designation by the US Food and Drug Administration (FDA) for fast-track evaluation as a potential antiepileptic [32].

Designer Δ^9-THC analogs other than nabilone, including n-hexyl-Δ^{6a}-THC and the hydroxyl analog of 1,2-dimethylheptyl-THC (HU-210), have been tested in humans but have not received regulatory approval (Fig. 6.1) [28, 33]. The first new chemotype distinct from THC ushered in the aminoalkylindole class of cannabinergic ligands, of which AM2201 is a typical example (Fig. 6.1), that may show preclinical antinociceptive activity (Fig. 6.1) [34]. Unfortunately, illicit recreational drug use of aminoalkylindole cannabinoids ("fake cannabis" or "synthetic marijuana" marketed as herbal preparations under trade names including "K2," "Spice," "Buzz," "Black Mamba"), most of which are DEA Schedule-I controlled substances with no approved medical use, has obviated interest in their potential therapeutic value [35]. The high abuse potential of such products relative to Δ^9-THC reflects their typical pharmacological profile as potent, high-efficacy CB1 full agonists, whereas Δ^9-THC is a CB1R partial agonist [36, 37].

Other synthetic cannabinoid agonists are widely used in the laboratory. Prominent among these pharmacology tool compounds are the aminoalkylindole derivative and high-affinity CB1R full agonist WIN 55,212–2; the full CB1R and CB2R agonist CP-55,940; and the metabolically stable, methylated AEA analog, (*R*)-methanandamide (AM356) (Fig. 6.1) [2].

CB2R Agonists

The virtually exclusive peripheral localization of CB2R under normal physiological conditions and the ability of CB2R activation to exert antinociceptive and anti-inflammatory action without the adverse central effects associated with CB1R activation stimulated the design and pharmacological profiling of synthetic CB2R agonists as potential therapeutics [38]. Among the most effective CB2R agonists are the aminoalkylindole AM1241 and the cannabilactone AM1710 (Fig. 6.1), both of which display preclinical efficacy in rodent models of inflammatory and neuropathic pain [39, 40]. AM1710 may also behave as a low-potency, low-efficacy competitive antagonist in certain signaling pathways [41]. Despite such preclinical efficacy data for pain relief, human studies of CB2R agonists as potential analgesic agents have not yet yielded marketed therapeutics mainly due to suboptimal clinical efficacy for indications tested [42], relegating AM1241, AM1710, and some other CB2R agonists to the role of laboratory tool compounds. The isotopically labeled CB2R agonist, [^{11}C]-GW-842,166X (Fig. 6.1), has been used as a positron emission tomography imaging tool for studying drug biodistribution and visualizing CB2R in humans [43].

CB1R Antagonists

The first reported CB1R antagonist/inverse agonist, SR141716 (rimonabant), is a biarylpyrazole capable of blocking cannabis(-like) effects elicited by CB1R agonist activation and, by virtue of its inverse agonist property, inhibiting CB1R constitutive (i.e., ligand-independent) signal transmission (Fig. 6.1) [44]. Launched in Europe as an adjunctive weight-loss therapy after demonstration in multicenter international human trials of its anorexigenic effects, post-marketing data revealed adverse gastrointestinal and psychiatric adverse events in a subset of patients that led to manufacturer removal of the product from the European market and withdrawal of the rimonabant New Drug Application from the FDA. Rimonabant's neurobehavioral side-effect profile and market withdrawal caused several other companies to abandon summarily their development programs on other, structurally distinct "-abant" CB1R antagonists/inverse agonists as potential weight-loss and smoking-cessation drugs [45]. Nonetheless, novel CB1R antagonists are used as imaging agents for studying diseases whose etiology may involve hyperactive CB1R activity, as exemplified by the first-generation CB1R antagonist/inverse agonist and rimonabant analog, [^{123}I]-AM281 (Fig. 6.1) [46].

Preclinical evidence suggests that at least some of the adverse gastrointestinal, neurological, and behavioral effects of high-affinity CB1R antagonists/inverse agonists such as rimonabant may reflect their inverse agonist property, i.e., their ability to inhibit the relatively high, physiological levels of constitutive CB1R signaling in the CNS, thereby eliciting opposing pathological responses [47–49]. With the aim of developing more drug-like agents having reduced potential for undesirable CNS side effects, design efforts have been focused on small-molecule CB1R antagonists characterized by weak, if any, inverse-agonist action (so-called "silent" or "neutral" antagonists) [47, 49] and/or CB1R antagonists/inverse agonists with limited CNS exposure/activity [47, 49, 50]. Examples of this approach are the periphero-neutral CB1R antagonist, AM6545 (Fig. 6.1) [51], and the centrally acting neutral antagonist AM4113 [52].

CB2R Antagonists

Preclinical data suggest that CB2R antagonists/inverse agonists could be beneficial as immunomodulation therapies and as treatment against bone loss [53, 54]. Lacking a wide range of potential indications to which they may be applied clinically, synthetic ligands with CB2R-antagonist activity such as the CB2R inverse agonist AM630 have been utilized primarily to study CB1R/CB2R selectivity requirements or to interrogate structural features of the CB2R ligand-interaction profile. For example, the biarylpyrazole CB2R antagonist/inverse agonist AM1336 (Fig. 6.1) has been used as a site-directed covalent probe for defining critical amino acid residues in CB2R's orthosteric ligand-binding domain [55].

Indirectly Acting Cannabinoid Agonists: Inhibitors of FAAH, MGL, and AEA Transport

Inhibitors of the endocannabinoid-degrading enzymes MGL and FAAH may be considered indirect cannabinoid agonists, since attenuating the activity of these enzymes should effectively increase tissue endocannabinoid tone *in vivo* [22, 23, 25]. Likewise, inhibitors of carrier-mediated AEA removal from the synaptic cleft may indirectly potentiate presynaptic CB1R-mediated signaling [56]. First-generation FAAH inhibitors were designed by incorporating strategically placed reactive groups capable of forming a covalent bond by sulfonylating the enzyme's nucleophilic catalytic residue, Ser241. This design strategy is exemplified by sulfonyl fluoride electrophiles such as AM3506 that irreversibly inhibit the enzyme with considerable selectivity (vs. MGL) (Fig. 6.1) [57]. Structurally diverse carbamate derivatives such as URB-597 also exemplify this design approach, acting irreversibly by their ability to carbamylate active-site Ser241 (Fig. 6.1) [58]. In rodent models, FAAH inhibition by active site inhibitors including AM3506 has been reported to elicit salutary anxiolytic, antihypertensive, antinociceptive, and gastrointestinal motility effects potentially useful for treating disease (e.g., [59]). However, the pain relief from FAAH inhibition observed preclinically did not translate successfully into the clinic [22, 60]. Detailed discussion of later-generation chemical classes of FAAH inhibitors and their pharmacological profiles may be found elsewhere [22, 25].

As with FAAH, numerous MGL inhibitors of various structural classes have been designed and profiled, and their structures and biological effects *in vitro* and *in vivo* have been reviewed [10, 22, 25]. The majority are carbamate or urea derivatives that target the enzyme's catalytic site or Michael-addition acceptors with the ability to react covalently with (a) sulfhydryl-sensitive cysteine residue(s). Although beneficial effects of selective pharmacological MGL inhibition have been reported (e.g., analgesia, antinociception) [10, 25], at least some MGL inhibitors have been associated preclinically with adverse responses including cannabimimetic effects, functional antagonism of brain CB1R leading to anxiety and depression, and altered synaptic transmission sufficient to compromise memory function [61–63]. These potential development liabilities have largely shifted the utility of MGL inhibitors as laboratory tool compounds or covalent MGL probes for interrogating the enzyme's catalytic mechanism and structure [64].

Some two decades ago, AM404 (Fig. 6.1) was reported as among the earliest examples of a small-molecule inhibitor of AEA reuptake, a property that would serve to increase endocannabinoid content in the synaptic cleft, thereby supporting enhanced CB1R-mediated signaling [65]. Subsequent data showing that AM404 can also activate transient receptor potential cation channel subfamily V member 1 (TRPV1), inhibit cyclooxygenases 1 and 2, and evidence CB1R-independent activity require caution in ascribing the entirety of AM404's biological effects (e.g., anticonvulsant, antinociceptive, antidepressant, anti-addiction, neuroprotective) to activation of the endocannabinoid system [66, 67].

Endocannabinoid-System Pharmacological Modulation to Treat CUDs

Cannabis remains a Schedule-I substance, despite successful marijuana legalization efforts of late. As recently reviewed elsewhere, various drugs of diverse therapeutic classes have been evaluated in preclinical models, human laboratory, and clinical placebo-controlled treatment studies over the last decade as potential pharmacotherapies for CUD's clinical manifestations, particularly cannabis withdrawal and relapse [68–72]. The tested agents include a wide range of substances chosen principally because of their known ability to attenuate mood and behavioral symptoms (irritability, depression, anxiety, insomnia, attention deficit) associated with continued cannabis use: antidepressant noradrenergics, anxiolytic serotonergics, antipsychotics, antiepileptics, mood stabilizers, mu-opioid receptor antagonists, and *N*-acetylcysteine. Translational success has eluded these efforts. There is at present no FDA-approved pharmacotherapy for directly treating CUD. The unsatisfied medical need represented by CUD is underscored by the fact that cannabis is the most commonly used illicit psychoactive substance worldwide, with some 12% of regular cannabis users – if not more – progressing eventually to clinically significant CUD [73, 74].

As demonstrated by the foregoing consideration of the molecular basis of the endocannabinoid system and its modulation, endocannabinoid signaling can be potentiated or attenuated pharmacologically by structurally diverse designer small molecules targeted to the most well-studied endocan-

nabinoid-system GPCRs (CB1R and CB2R) or the enzymes primarily responsible for terminating endocannabinoid signal transmission (MGL and FAAH). Targeted modulation of endocannabinoid-system activity has also been examined as a modality for treating SUD. Reflective of the critical role of CB1R activation in the psychobehavioral effects of cannabis/Δ^9-THC, most cannabinoid-related approaches aimed at identifying potential CUD treatments have focused primarily on pharmacotherapeutic CB1R modulation [69–72, 75].

The following discussion focuses on data modes of endocannabinoid-system pharmacological modulation with promise for the design and development of novel CUD medications.

Treating Acute Cannabis Toxicity

Cannabis edibles are readily available in the increasing number of locales where cannabis has been legalized for recreational/medicinal uses [76, 77]. Unintended ingestion of large quantities of highly palatable cannabis products (e.g., brownies, cookies, candies) by children and young adults is a serious public health concern [78–81]. The resultant, acute cannabis toxicity may elicit nonspecific effects (e.g., lethargy, reduced muscle strength/paralysis, tachycardia, nausea, hallucinations, paranoia, dry mouth) and (more rarely) encephalopathy and coma requiring emergency room attention or admission to the intensive care unit [36, 80, 82–85]. The steadily increasing potency of newer cannabis strains selectively bred to increase their Δ^9-THC content and the growing number of synthetic cannabinoid street drugs typically more potent than Δ^9-THC itself and of un- or ill-defined chemical compositions have exacerbated the potential for toxic cannabinoid effects more serious than from traditional milder marijuana strains [35, 86]. Given the likely increased incidence of cannabis toxicity as legal medical and recreational marijuana use becomes more widespread [77, 87], profiling of CB1R antagonists in preclinical models of acute cannabis toxicity is warranted.

Synthetic CB1R full agonists sold illicitly as recreational drugs can cause significant intoxication and toxic effects including psychosis, anxiety, depression, and even death [36, 80, 82, 83, 85]. A recent report demonstrates that cannabimimetic effects (hypothermia, sedation) of the high-potency, high-affinity synthetic CB1R agonist CB-13 in mice are rapidly reversed by acute administration of the CB1R antagonist/inverse agonist AM251, a close structural analog of SR141716 (rimonabant) (Fig. 6.1) [88]. This preclinical result suggests that an immediate-release, single-application oral CB1R receptor antagonist/inverse agonist could act as a "rescue" antidote to reverse cannabis intoxication, an approach actively being pursued by the authors. Of note, CB-13 (otherwise designated as SAB-378), a peripherally acting CB1 agonist with limited brain access [89], typically showing CNS related effects only at very high doses, was used in this study. Ref. [89]. Moreover, unlicensed recreational preparations of brain penetrant synthetic CB1R agonists, lacking proper toxicological and chemical characterization, usually consist of mixtures of ill-defined substances, some of which may themselves exert toxicity *independently* of CB1R and/or the endocannabinoid system [35, 90]. Thus, it remains to be determined whether whether a selective CB1R antagonist/inverse agonist will therapeutically antagonize all the neurotoxic effects of "Spice" and other synthetic cannabinoid street drugs.

Despite encouraging preclinical data, the potential association of CB1R inverse agonism with adverse psychobehavioral effects (anxiety, worsening depression with suicidality) as observed clinically with rimonabant suggests that a short-acting CB1R neutral antagonist may be more attractive for treating the acute toxic effects of cannabis. Congruent with this contention, in rats the novel CB1R neutral antagonist AM4113 has shown preclinical therapeutic efficacy like rimonabant's for nicotine dependence, but with better psychiatric tolerability (i.e., less anxiety/depression-like effects) [91].

Treating Chronic CUD

The primary clinical goals of treating any chronic substance use disorder are to decrease (if not halt) drug use, reduce withdrawal symptoms, establish behavior control, and prevent cravings that could incite the vicious cycle of repeated abstinences interspersed with relapses [92]. As exemplified by methadone and buprenorphine for treating opioid-use disorders and by the nicotine transdermal patch, substitution therapy is well established as a means of transitioning from uncontrolled substance abuse to regulated use in the progression toward durable abstinence [93]. Regarding CUDs, most investigations on substitution therapy have examined the (pre) clinical efficacy of the marketed CB1R agonists Δ^9-THC, dronabinol, nabilone, and nabiximols (and its CBD constituent) as potential CUD monotherapy – or, in select cases, when combined with the short-acting antihypertensive lofexidine used to allay symptoms of opiate withdrawal or the sedative zolpidem used primarily to aid sleep. As detailed, the outcomes of clinical studies of CB1R agonists as CUD treatments are mixed [69–72, 94]. The most positive data from human laboratory studies and one fully powered clinical trial suggest that high-dose dronabinol might be effective for relieving cannabis withdrawal symptoms, a clinical response important for reducing cannabis use and initiating abstinence [95, 96]. Yet there has been a general failure of substitution therapy with CB1R agonists at safe and well-tolerated doses to decrease relapse or promote durable abstinence in the clinic, notwithstanding limited laboratory and clinical results suggesting that nabilone may hold some promise in this regard.

An alternative therapeutic strategy for increasing endocannabinoid tone to therapeutic levels involves inhibiting the principal enzymes, MGL and FAAH, that degrade the highly labile endocannabinoids 2-AG and AEA, respectively. This indirect approach has met with demonstrated preclinical success in offering site- and event-specific neuroprotection in models of traumatic brain injury, excitotoxicity, seizures, and multiple sclerosis [23]. Advantageously, the use of MGL/FAAH inhibitors to potentiate endogenous CB1R signaling would allay potential drawbacks associated with direct CB1R agonists as substitution therapy for CUD that revolve around the substituting agent's abuse liability. This latter distinction is underscored by recent preclinical demonstration in nonhuman primates that the therapeutic effects of selective enhancement of 2-AG or AEA activity with MGL or FAAH inhibitors does not incite CB1R agonist-like, abuse-related subjective effects. Administration of exogenous 2-AG or AEA also did not produce CB1R-mediated discriminative stimulus effects related to the CB1R full agonist, AM4054 (Fig. 6.1) [14].

CB1R antagonists also represent a tenable alternative to direct CB1R agonists for treating CUD, since their ability to block the subjective and reinforcing effects of Δ^9-THC in experimental animals and humans is well-established [97, 98]. Antagonist-based strategies have ample precedent for treating other use disorders (e.g., naloxone as antidote for acute opioid overdose) [99]. Many CB1R-selective orthosteric antagonists with diverse chemotypes have been synthesized over the past 20 years, and several have been profiled preclinically for varied indications [45, 100]. In this regard, data on the influence of the CB1R-selective antagonist/inverse agonist rimonabant (Fig. 6.1) on nicotine addiction are particularly relevant. Rimonabant has demonstrated preclinical efficacy in decreasing nicotine-taking and nicotine-seeking and attenuating nicotine-induced dopamine elevation within primary brain reward areas (e.g., nucleus accumbens). In randomized clinical trials, rimonabant dose-dependently improved the ability of smokers to quit smoking by some 1.5-fold, increased their likelihood of remaining abstinent, and moderated their cessation-associated weight gain [101, 102]. These clinical results with nicotine-use disorder suggest that CB1R antagonist therapy can attenuate neuronal pathways involved in both drug-taking behavior and relapse phenomena (reward, reinforcement). The suggestion is borne out by preclinical demonstration that rimonabant blocked THC-seeking behavior and reinstatement behavior/relapse to nicotine and cannabis in nonhuman primates as well as data from human laboratory studies that both a single high dose (90 mg) and repeated lower doses (40 mg each) of rimonabant attenuated the subjective and physiological effects of smoked cannabis [98, 103, 104]. However, post-marketing data associating rimonabant, at effective anorexigenic doses, with mood-altering side effects that could lead to suicidal ideation effectively ended rimonabant's potential regulatory approval for any indication, including CUD [45]. The relevance of CB1R antagonists/inverse agonists' clinical efficacy for nicotine addiction to CUDs is underscored by the human laboratory finding that tobacco smoking status is a robust predictor of marijuana relapse, suggestive of a pathogenic component of incentive salience shared by nicotine and cannabis abuse that may be therapeutically exploitable by CB1R blockers to treat CUDs [105].

Rimonabant's adverse psychological effects may reflect, at least in part, its ability to inhibit CB1R constitutive (i.e., ligand-independent) activity through its inverse-agonist property and thereby incite responses opposing the physiological [45]. Given their lack of inverse-agonist activity, CB1R neutral antagonists may represent an alternative therapeutic approach to standard CB1R antagonists/inverse agonists for substance use disorders [47]. This suggestion is strengthened by observation in nonhuman primates that the CB1R neutral antagonist AM4113 reduced two effects of nicotine and Δ^9-THC that may play major roles in tobacco and cannabis dependence: maintenance of high rates of intravenous drug-taking behavior and, in relapse models, reinstatement of drug-seeking behavior [106]. Demonstration that AM4113 can block nicotine and cannabinoid reinforcement suggests that CB1R neutral antagonists could represent a novel class of medications for both tobacco dependence and CUD.

Conclusion and Future Perspectives

Improved understanding of the molecular basis of cannabinoid activity and the function of the endocannabinoid signaling system in health and disease suggests new ways of targeting system constituents with small-molecule modulators to treat both acute cannabis intoxication and more chronic CUDs. Emerging data support conclusion that CB1R neutral antagonists hold promise for treating the acute toxic effects of cannabis and CUD while avoiding the psychobehavioral and gastrointestinal liabilities of typical CB1R antagonists/inverse agonists. Although some positive clinical data have been reported for direct CB1R agonists as CUD substitution (mono)therapy, inconsistent efficacy results leave the question open as to whether CB1R agonists could be truly effective as population-based CUD medications. Risks associated with CB1R-agonist substitution therapy make enhancing endocannabinoid tone indirectly by inhibiting the principal 2-AG and AEA degrading enzymes, MGL and FAAH, respectively, a potentially safer and attractive CUD therapeutic approach. The demand for therapeutically exploitable CUD treatments in the face of increasing societal

and legal acceptance of cannabis warrants continued preclinical profiling of CB1R neutral antagonists and MGL or FAAH inhibitors in clinically relevant CUD models.

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Translation of CUD Therapeutics from Drug Discovery to the Clinic

7

Aidan J. Hampson and Robert L. Walsh

Introduction

Are We There Yet: Why Is It Taking So Long?

This chapter examines what approaches have been used to treat CUD to date and notes that they seem to be based on analogous disorders and clinical symptomology. In the second decade of the twenty-first century, this seems oddly anachronistic, and so the chapter examines what it takes to transform a fundamental discovery into a testable medication. Attempts are made to shine a light on the somewhat occult practices and work patterns involved in medication development. However, these practices are common to all translation pharmacology, and therefore do not explain why CUD therapeutics have developed so much more slowly than other pharmacotherapies, particularly by comparison to opioid use disorder therapeutics.

The authors suggest that together with legal and social restrictions, it is the physical properties of cannabinoids that slowed progress for more than 100 years. The authors provide a brief comparative history of opioid and cannabinoid pharmacology and note the relative Golden Age of cannabinoid pharmacology which is upon us now. The chapter concludes by discussing recent and ongoing clinical trials that have finally translated fundamental findings into candidate medications for cannabis use disorder.

Hit Expansion and Lead Optimization

The initiating sequence for many pharmaceutical development programs is the identification of a "target," the association of a protein's (receptor/enzyme) role in a disorder, and a "hit" in the discovery of an agent that will modulate the target's function. The "hit" represents a potential leverage point, but the probability that the initial hit compound will become a medication is very low; due to the sheer number of criteria a lead compound must meet prior to human testing, even before examination of its clinical efficacy. To illustrate this issue, there follows a broad-strokes discussion of many of the issues involved in developing a lead compound.

The first stage of drug development is often the structural modification of a hit molecule to increase its chances of success. This process, often described as "hit-to-lead optimization," attempts to identify the key elements of the structure, along with rectifying weaknesses in the prototype and avoiding predictable pitfalls. Concerns may be addressed by altering the medication dosage form, i.e., using formulations to mitigate concerns, but this is typically a late-stage strategy to support a suboptimal compound. At the beginning of a drug development program, it is more common to optimize the final product by establishing what structural motifs of the initial hit are required for activity and what parts are a liability. This is an iterative process of modification and followed by testing in one or more assays, known as hit expansion or later as lead optimization.

Rational Design Versus High-Throughput Screening

Commonly a hit expansion program to develop lead candidates is accomplished by examining the structure-activity relationship (SAR) of the chemical "space." This involves considering the hit molecule as a scaffold and making a sequential series of changes, for example, attaching alkyl groups of different chain length. The analogs are then assayed to determine which chain length provides optimal potency without disrupting other parameters such as solubility or increasing activity at unintended off-target sites. Such a strategy is commonplace and represents a "rational design" process that is heavily dependent on the skill of your medicinal chemists and somewhat dependent on good fortune. In the first decade of the twenty-first century, a different hit expansion ethos gathered popularity, based on a couple of key technological innovation(s). Combinatorial Chemistry uses a series of defined chemical units, which can be mixed

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and matched much like toy bricks to generate a large number of product variants in a single step [1]. This process allowed creation of very large (sometimes compounds multiple millions strong) chemical libraries. At around the same time, high-throughput screening (HTS) processes were developed to leverage the capacities of combinatorial chemistry. Given that robotic HTS fluorimetry and electrophysiological patch-clamp systems can rapidly conduct 96 or 384 assays in a single plate of cells cultured to express a target protein [2], together these systems allowed drug development programs to rapidly examine very large chemical spaces. However, while HTS is less reliant than rational design on serendipity and/or excellent medicinal chemistry, such brute-force programs are expensive and generate a lot of waste. Worst of all, HTS programs did not live up to initial expectations in the numbers of resultant FDA-approved drugs. Consequently, when resources in the pharmaceutical industry came under pressure after the financial crash of 2008, HTS became more selectively implemented [3].

Overall Rationale Behind Development Programs

Programs with exceedingly large numbers of potential hits such as those using HTS techniques provide an inflated example of the situation that even small rational design programs also have, i.e., how to select molecules from a field of competitors, each of which has potentially different strengths and weaknesses in different analog assays. The two most basic tools used to manage such programs are the prioritization of assays and assignment of minimal/maximal acceptance values to each assay. The former process seeks to preserve precious resources while the latter serves to convert analog datasets into digital go/no-go values that are easy to compare, even if detail/nuance is lost.

Assay prioritization uses rapid assays, such as calcium fluorimetry in 96-well plates expressing cloned receptors, or the rate of compound metabolism by liver microsomes, to promote or eliminate candidates as inexpensively as possible. Such assays are generally arranged as a series of "filters," to confirm desirable and reject undesirable features (counter-screening) in compounds, so that only the most promising hits progress to costly later-stage studies. An important element when constructing filter tiers is prioritization of assays central to the project development (sometimes described as the "critical path") while allowing other perhaps more interesting but less critical studies to be put on a slower schedule.

Each program will have its own set of strengths and weaknesses, although there are many common issues in drug development which usually/always need to be addressed. The typical areas of concern can be divided into pharmacodynamic examinations and studies examining "drugability." The latter is a jargon term that refers to optimizing the initial hit compound's physicochemical and pharmacokinetic (PK) properties. Improving drugability can mean specific modifications to improve the compound's solubility and chemical stability but also covers the more general studies such as looking at metabolic stability.

Metabolic Stability or Absorption, Distribution. Metabolism and Elimination (ADME) studies examine drug absorption and availability at target and other tissues, and considers the major metabolites formed and the route(s) and speed of drug elimination. It is important to be aware that metabolites can introduce their own liabilities, such as off-target toxicity, or may turn out to be even being more potent drugs than their parent molecule. If this occurs, exposure to active drug moieties can very enormously depending on the individual's drug metabolism phenotype. In addition, ADME may vary substantially in different species, an issue because drug candidates need to be safe and suitably persistent in both humans and the preclinical animal models that will be used to demonstrate safety prior to "first in human" exposure. A drug predicted to give good exposure in humans but eliminated quickly in rodent models may be difficult to test for efficacy and will also be problematic to demonstrate as safe in toxicology studies, which require extended exposure. For this reason, preliminary rodent PK may be conducted early in the development process, while concern for predicting and characterizing human PK and metabolites may be reserved for later-stage development.

The second key area for study during hit expansion and later lead optimization studies is pharmacodynamic optimization. In addition to examining the drug's affinity (potency) and its efficacy/intrinsic activity (the degree to which it activates the target after binding), its selectivity, i.e., what other targets your hit affects, is also important. If examined early in the development process, highly problematic off-target sites of action can be subject to counter-screening as a key early-stage "filter." Similarly, a broad-spectrum screen of the final lead "contenders" can ensure that no off-target effects have been inadvertently introduced and assist in prediction of adverse clinical effects and the safe upper limit for clinical dose development.

Recent Considerations for Drug Development

Over the last few years, previously unrecognized pharmacodynamic properties of G-protein-coupled receptors (GPCRs) have been revealed that both complicate and promise new vistas in drug development. The previous view was that GPCRs (e.g., cannabinoid receptors) transduce a signal from the exterior to interior of the cell following activation, by release of G-protein complexes, e.g., Gs or Gi/o or Gq classes. Receptors were thought to be specifically associated with a G-protein class; e.g., cannabinoid receptors would interact with different members of the Gi/o class. The signal from each individual receptor was thought to be brief and terminated by receptor internalization, triggered by binding

of a beta-arrestin "flag" to the receptor region previously occluded by the now-liberated G-protein. Recently it has been found that some agonist-receptor complexes internalize with the agonist still attached and that the GPCR complex can continue to signal from within the cell for a prolonged period [4]. Such prolonged signaling after internalization suggests that the period over which an agonist remains associated with a receptor (a ligand's "off-rate"), may have at least as much pharmacological relevance as its overall affinity (Kd) [5]. Previously affinity and off-rate may have tended to be conflated as affinity is the ratio of on and off-rates and for many drugs the on-rate is primailry defined by its concentration (mass action). However, the finding that receptors with tightly bound ligands can continue to signal even after internalization, changes the has great implications for the pharmacodynamic/pharmacokinetic relationships; agonists with a slow off-rate may internalize and continue to generate responses even after the mass of drug has been cleared from the plasma. Furthermore, such drugs might well be expected to exhibit differential pharmacology when initially administered than at later time points as the signaling pathways change.

A second "clarification" that is revolutionizing pharmacology is the nature of beta-arrestin signaling. Rather just being a mechanism for signal termination, beta-arrestins induce their own intracellular kinase signals, and various ligand analogs for a single receptor may differ in their "bias," with respect to activation of G-proteins and arrestin pathways [6]. It is now becoming clear that systems are even more flexible; some ligand-receptor complexes not only show variable bias for arrestins versus G-proteins but also a particular ligand for a receptor may preferentially activate a different G-protein than other ligands [7]. It is hypothesized that such complexities create activity "fingerprints" that are distinctive for each ligand and receptor. It is certainly possible that this flexibility may contribute to the different properties of drugs that were thought to act via the same few signaling pathways (e.g., cannabinoid and opioids).

These new paradigms present the potential to design ligands with specific signaling that may separate desirable and deleterious receptor functions. There is evidence that beta-arrestin-biased beta-adrenergic agonists are superior as sustained promotors of cardiomyocyte survival [8], while mu-opioid ligands with reduced arrestin signaling show analgesia, but with slower drug tolerance development [9]. One might reasonably presume that the relative abundance of different signaling components in a cell type (particularly heterologous cells engineered to express a specific protein) would influence the apparent pharmacology of tested ligands and so results may vary in different cell lines and tissues. Clearly then, one must be aware of whether screening assays chosen, accurately recapitulates the clinical tissue targeted and whether the observed responses represent effects in certain tissues or species. Results from an assay validated as a clinical predictor for one drug series may not hold true for another series and so it is important to choose screening models with care and perhaps add verification assays to screen prior to investing too heavily in promising lead compounds.

Assimilating Imperfect Data Sets and compromise; Drug Development Skills

A medicinal chemistry program may develop hundreds to thousands of molecules to be tested in a range of different assays, and the data needs to be integrated before lead selection; it is therefore almost inevitable that compound A may be superior to compound B in one assay but inferior in other aspects. Furthermore, there may be missing datasets and almost certainly there will be variability in the degree to which positive and negative controls responded on a given day. In other words, hit-to-lead development requires decisions to be made based on arrays of imperfect analog data sets. The central mission of development is not data perfection, but the accurate choice of lead selection and development as rapidly and inexpensively as possible. This means that the mental workflow patterns involved in drug development are quite distinct from those required by discovery scientists. The latter profession requires attention to detail, testing, and retesting findings in overlapping and redundant ways, as well as consideration of alternative interpretations and how to confirm or disprove hypotheses. Drug development requires a more expansive view to select a lead compound that may not be optimal in all regards. To synthesize the outcome of many analog data sets with variable daily responses requires an almost "fuzzy logic." Considering the number of criteria to be assessed, success in development cannot afford any more than necessary assay redundancy, nor the time to examine why a compound acted in a peculiar manner. Development necessitates almost obsessive degree of standardization, establishment of a well-defined critical path, and a laser focus on the ultimate aim, i.e., to advance one or two compounds to the clinic with maximal financial and temporal efficiency.

The twin goals of the critical path, a logical tiering of "filter" assays and resource preservation, sometimes come into conflict. For example, it is logical to confirm that a compound provides sufficient PK exposure to ensure a pharmacological effect in your animal model, prior to conducting efficacy studies. However, if PK studies cannot be performed in-house, they can be expensive and so reserved for advanced hits. An appropriate compromise might be to use in vitro liver microsome, cloned cytochrome P-450 proteins, or hepatocyte studies, to obtain a quick (and dirty) prediction of the expected degree of pharmacological exposure of a number of compounds, instead of conducting full pharmacokinetic analyses. Similarly, instead of determining brain penetration

of a compound early in development, it may be appropriate to equate changes in animal behavior as a readout of pharmacological activity and brain penetration. Such shortcuts would not be acceptable for publication of rigorous discovery studies in top peer-reviewed journals, but may suffice to reduce the shortlist of potential lead compounds. These examples illustrate the types of compromise that are the signature of critical path drug development, the need to whittle down a large number of potential candidates using multiple criteria, in a minimal amount of time while preserving resources for later expensive studies.

Lead Development

Once a lead compound has been identified with demonstrated efficacy, satisfactory drugability and PK exposure, and a large enough apparent "therapeutic index," i.e., the ratio between the doses required for therapeutic and toxic effect, study emphasis may move to preparation for clinical testing. During this stage, known as lead development, the leanness of critical path studies remains the mantra, but the process of generating and eliminating candidates stops (or slows), in favor of focusing on the Lead (and hopefully at least one backup molecule). Unexpected problems can always derail a lead, and the "fail early, fail cheap" mantra requires alertness for signs of failure. It is therefore always desirable to identify backups to the lead compound and maintain their development on a parallel track to the lead, perhaps waiting at an expensive gating juncture. Given that a failure in a lead is more likely to also occur in a similar backup molecule, it is optimal to have your backups be as structurally dissimilar to the lead as can be achieved, while also optimizing other characteristics. Obviously, this is easier to say than to achieve.

Lead development studies aim to generate data which demonstrate the potential medication is safe, can be reliably manufactured, and is stable in a clinically acceptable formulation. When clinicians submit an investigational new drug (IND) application to the FDA, to seek approval to test the lead compound in "first-in-human" studies, the information generated by the lead development studies accompanies their proposed clinical protocol. Alternatively, if the company does not wish to share all of the information with the investigator (e.g., that related to chemical synthetic pathways), they may file a Drug Master File (DMF), containing all of the appropriate data directly to the FDA. In this case, the company or DMF Holder supplies investigators with a "letter of authorization" (LOA) to cross-reference the DMF in their IND submission.

The LOA allows the DMF holder to facilitate investigators or companies to use the DMF information to support their FDA filings without revealing all of the information contained within. One of the key sections of the DMF generated during lead development is the CMC section, or "chemistry, manufacturing, and controls" section. This contains information on the actual compound, such as how it was made and its purity, and the formulation(s) of the drug and placebo product(s) as well as an environmental analysis of the effects of the drug on the environment.

The DMF also contains evidence of the drug's preclinical efficacy and animal toxicology (safety) studies of appropriate length to support at least the Phase 1 clinical studies. The toxicology studies need to be based on the multiples of the degree of exposure expected in the clinical studies, and so the DMF also needs to provide PK data examining the formulation in at least two animal (one non-rodent) models. The models chosen should include the species used in the toxicology studies, in order to confirm appropriate exposure to the drug during the safety trials. The PK studies generally demonstrate the absorption and elimination of the parent molecule and its major metabolites, as well as characterizing the metabolites and ideally the enzymes responsible for metabolite synthesis.

Given the time and costs associated with lead development, it is wise to seek a "pre-IND" meeting with the FDA. This meeting would propose and seek feedback on a suite of studies that would provide the FDA with all of the data needed to ensure a successful IND application. Given the change in emphasis, during lead development, expenditures increase significantly. The necessary wide-ranging studies (not to mention industrial drug synthesis) require a considerable variety of skill sets and so in many cases must be outsourced to third-party contract research organizations. These organizations not only specialize in doing the studies necessary to support a strong IND application but also conduct them according to the data recording and auditing standards associated with current FDA good laboratory practices (GLP), good manufacturing practices (GMP), and good clinical practices (GCP.) Technically speaking, the requirements for Phase 1 and 2 studies may not require all of these standards to be exactly followed, but it may be in the best interests of the IND holder to look ahead to the needs for Phase 3 where full GMP material will be required. In addition, having the toxicology and stability studies performed on GMP-grade product strengthens the IND application and avoids the potential need for bridging and/or additional toxicology studies being needed in the future. Given the increasingly escalating costs of lead development studies, it is clear why a backup molecule is developed at a slower pace than the lead molecule.

History of Drug Development for Cannabis Use Disorder

The section above is intended to outline a typical translational endeavor that takes place between "hit" discovery and clinical testing of a new drug. This is included because medication development generally takes place in the proprietary, confidential environment of corporate organizations,

and so the scale of the endeavor and the workflow patterns involved are not always widely understood by the public or even by academic discovery researchers and clinicians. The format described represents a rational and efficient manner to get from "hit" discovery to a viable product for clinical testing, or to kill a failing project as early as possible. However, clinical investigations to develop therapeutics for CUD have not typically been sponsored by the pharmaceutical industry, but have been the domain of academic research groups. As such, rather than developing and testing new molecular entities derived from fundamental discoveries about function of the endocannabinoid system (ECS), CUD clinical studies have mostly attempted to repurpose existing medications. The hypotheses underlying the majority of CUD clinical studies to date have largely fallen into three categories. These are agonist replacement therapeutics; medications with convergent construct validity, i.e., drugs with activity in other SUD conditions; and finally treatments intended to relieve cannabis use(r)-associated symptoms.

The principal rationale for cannabinoid agonist substitution in CUD has been to reduce cannabis smoking-associated harms. These harms include smoking-related medical concerns but also extend to health issues arising from legal jeopardy and employment problems *meta* to the consumption of illicit substances. The US pharmacopeia contains two cannabinoid agonists, and both have been examined as agonist replacement therapies but were first approved for treating chemotherapy-induced nausea. The first of these is dronabinol, which is defined as synthetic (not plant-derived) THC in a capsule of sesame oil [1]. The other cannabinoid agonist is nabilone, a synthetic derivative of THC sold under the brand name "Cesamet" [2]. The pharmacokinetic half-life of nabilone is similar to THC, but with purportedly higher bioavailability. However, while orally consumed THC is largely converted to 11-hydroxy-THC during absorption [3], this metabolite is equipotent to THC at CB1 [10], so dronabinol is pharmacodynamically more active than its bioavailability might suggest.

The second category of medications examined as CUD treatments is based on compounds with efficacy in other SUD indications. The logic is that we have defined reward pathways, and so perhaps rewarding drugs may have overlapping points of intersection. Naltrexone is an example of such convergent construct validity, as applied to CUD treatment. This oxymorphone-derived opioid receptor antagonist was initially approved to block the rewarding effects of opioids but subsequently was shown to have a degree of efficacy in treating alcohol dependency [11]. Given that such efficacy suggests an involvement of opioid receptors in multiple SUD states, naltrexone has also been tested in human lab studies of CUD [12]. The category of symptomatic relief of psychiatric symptoms associated with cannabis use [13] and withdrawal (e.g., depression, anxiety, and insomnia [14]) has frequently been used as a basis for experimental studies of CUD treatments. The number of medications tested under this paradigm is fairly long but includes a range of antidepressants and mood stabilizers [15].

Why Are Clinical CUD Studies Not Derived from Fundamental Science?

To an observer from outside the CUD field, it might seem surprising that clinical studies have not principally relied on a fundamental understanding of the ECS. It takes time for discoveries to result in investigational new drugs, and this is true for all medication development. However, most medication development fields have not been subject to the same regulatory barriers as cannabis research, barriers which have historically affected not only the conduct of cannabinoid research but also its perception. To some degree these barriers may explain the pharmaceutical industry's reluctance to develop CUD medications, but the field also lacks a strong patient advocacy community calling for CUD therapeutics.

At the present time, the perception of cannabinoid research as "serious science" has much improved, and societal restrictions on cannabis use are diminishing. This deregulation inevitably will increase the number of users and of those who become dependent, but it also presents another conundrum. Many clinical CUD researchers are finding difficulty in recruiting subjects for CUD trials as the lifting of legal restrictions reduces public perceptions of harm and eliminates some of the motivation to address dependence issues. Together these factors continue to complicate definition of the market size for CUD medications. Despite these issues however, perhaps the most critical reason why CUD clinical studies have lacked a fundamental scientific underpinning lies in the slow and arduous development of understanding of the pharmacological effects of cannabinoids and endocannabinoid physiology.

A Brief History of Cannabinoid Pharmacology

A perspective on how slowly cannabinoid pharmacology has developed is well illustrated by comparing the recent history of cannabis and opium. At the first part of the nineteenth century, chemists were making great advances in isolating alkaloids from opium, with morphine being first isolated in 1805 [16] and the safer opiate codeine in 1832 [17]. Over the same time frame, Napoleon's army introduced French society to Egyptian hashish (circa 1802) [18, 19], and Dr. O'Shaughnessy reported the medicinal value of Indian hemp to the British Royal Society in 1841 [20]. As a result, both cannabis and opium derivatives made their way into numerous medications during the second half of the nineteenth century. But, while alkaloids like morphine could be isolated with little more than hot water, alcohol, and ammonia, cannabis remained a crude plant extract with an unknown principal for more than 100 years after that time. It was not until 1964 that two Israeli chemists identified tetrahydrocan-

nabinol (THC) as the psychoactive principal of cannabis [21], by which time the life-saving opioid antagonist naloxone had already been reported (Fishman 1961).

Opioid pharmacology continued to advance with the debut of the radioligand binding technique, which elucidated the mu-opioid receptor in 1973, [22, 23] 9 years after the discovery of THC. The development of this rapid, sensitive technique for characterizing receptors ushered in an era of receptor discovery [24], but cannabinoid receptors were not revealed so easily. The high lipophilicity and relatively low potency of THC made it unsuitable as a radioligand, and so the basis of cannabinoid effects remained contentious until 1988 when the brain cannabinoid receptor (CB1) was finally demonstrated [25]. Finally, this discovery allowed cannabinoid science to progress. Between 1988 and 1995, the CB1 endogenous ligands, anandamide [26] and 2-archidonylglycerol (2-AG) [27], were isolated, and a fatty acid amide hydrolase (FAAH) responsible for anandamide breakdown was identified [28].

This latter report also identified the first generation of FAAH inhibitors, setting the stage for medications based on manipulation of the endocannabinoid system (ECS). Equally importantly for understanding CUD, the first CB1 antagonist was developed in 1994 [29] and was immediately used to refute the false distinction that cannabis does not cause withdrawal unlike other rewarding drugs [30]. By 1995 suggestions that THC pharmacology was due to "membrane perturbation" had given way to understanding that cannabis contains a drug that mimics endogenous agonists and acts via a G-protein-coupled receptor not unlike the opioid/endorphin system [30, 31]. The role of the ECS still remained to be elucidated, but the first big advancement came soon after and was presented almost as a *fait accompli*. Research findings concerning an electrophysiological phenomenon known as "depolarization-induced suppression of inhibition" (DSI) were reviewed in 1995, but the agent responsible remained mysterious [32].

The phenomenon of DSI is the inhibition of presynaptic GABA release following a strong electrophysiological stimulation of GABAergic postsynaptic preparations. For the next 6 years, DSI was investigated and linked to synaptic plasticity, and in 2001, the mediator was identified as 2-AG produced by post-synapses and acting in a retroactive manner on presynaptic cannabinoid receptors [33]. Because DSI had been relatively well-described as a mechanism for reducing synaptic strength, this finding provided a "bolus" of information. The role of the ECS in cognitive management was consistent with the amnestic properties of THC and provided a rationale as to why monoacylglycerol lipase (MGL), the enzyme that breaks down 2-AG, is located on presynaptic terminals [34]. In contrast, the enzyme that breaks down anandamide (FAAH) is predominately found on the postsynaptic side, suggesting a distinction between the roles of anandamide and 2-AG [35].

It has since become clear that the ECS and anandamide in particular plays a key role in the homeostatic regulation of stress hormone signaling [36, 37]. It is currently hypothesized that while 2-AG predominantly acts as a rapid "phasic" regulator of synaptic activity, anandamide mediates a more continuous (tonic) effect on mood regulation [38]. Given that the predominant symptoms of cannabis withdrawal are irritability, anxiety, depression, and insomnia [14], this understanding of the ECS suggested that manipulation of anandamide levels may provide a potentially viable approach to reducing cannabis withdrawal symptoms. Indeed, a study using FAAH inhibitor PF-04457845 started in 2012 (NCT01618656) tests this hypothesis.

Although the initial investigational indication for PF-04457845 was as analgesic for osteoarthritis, its examination as a treatment for CUD can be said to be a clinical application of fundamental advances in understanding the ECS. Progress is continuing, and in 2014 THC was demonstrated to increase endogenous synthesis of pregnenolone, which in turn acts as a CB1 negative allosteric modulator (NAM) [39]. Pregnenolone is a steroid precursor, i.e., it is rapidly metabolized into agents that would disrupt steroid hormone function, and so Aelis Farma used it as a structural scaffold (a pharmacophore), around which more "druggable" compounds could be developed. Pregnenolone is a biased NAM; it inhibits THC's effect on kinases and mitochondrial CB1 receptors more than it inhibits other signaling pathways. Aelis is hoping that a biased CB1 NAM may antagonize the effects of THC without the dysphoric effects that limited the safety of CB1 orthosteric antagonists such as rimonabant. This drug development program has resulted in AEF0117, a bioavailable pregnenolone analog which is now in "first-in-human" clinical dose range testing (NCT03325595).

These studies, known as "Clinical Phase 1," will ensure that the planned top dose is tolerable, at least for a brief period. In the next step (Phase 2), the first signs of clinical efficacy will be determined. Phase 2 is the most challenging stage; it is there that most clinically tested medications meet their Waterloo. The Aelis Farma project is a shining example of high-speed drug development, but their underlying concept is distinctly cutting-edge; the efficacy of their first-in-class drug remains to be confirmed. Even so, whether AEF0117 succeeds or fails, it represents a significant break from the traditional bases for clinical CUD investigations; it is a medication designed specifically for CUD treatment.

Summary

This chapter has attempted to outline the number of steps required for a basic science discovery to translate into a drug candidate for testing in humans, as a partial explanation as to why so few CUD therapeutic strategies tested to date are directly derived from fundamental findings concerning the

ECS. However, such delays and hurdles are common to translational pharmacology, but in the case of CUD, there must be other reasons. Cannabis use disorder is based on reward behavioral systems, and clearly attempting to alter such a behavior with a medication alone would be naïve; considerations of the interactions of pharmacology with behavioral and social are paramount. However, while social, behavioral, and regulatory restrictions have posed significant difficulties, these issues are true for the sister field of opioid pharmacology, and yet there, fundamental science has provided medications to stabilize patients (e.g., methadone), reintegrate them into society (buprenorphine, naltrexone), and ease withdrawal symptoms (e.g., alpha2 adrenergic agonists). We have argued that one basic difference between these two fields boils down to physicochemical properties between opioids and cannabinoids. This difference slowed progress in understanding of cannabinoids for 100 years. However, over the last 30 years, cannabinoid pharmacology has leapt forward with increasing vigor as legal and social restrictions on cannabis lessen. We now have recognized and started to characterize the ECS, and finally we have started to translate this knowledge into new CUD treatment approaches.

The Aelis NAM and the Pfizer FAAH inhibitor are examples of experimental CUD therapeutics based on understanding of the ECS, but others will surely follow. An inhibitor of 2-AG breakdown by MGL is now in clinical testing for (Abide Therapeutics, NCT03138421), and at the very least, if an MGL inhibitor receives FDA approval, it will surely be examined as a potential treatment for CUD. New basic science has shown that like opioid receptors, CB1R is also prone to signal bias, and so molecules designed to harness this phenomenon are in development. Biased agonists hypothesize that we can harness some of the desirable effects of CB1R activation, without having to accept them all, but only time will reveal the extent of the truth [40].

Whatever new medications translate from the now burgeoning field of cannabinoid pharmacology, one thing is certain: they will need to address concerns that patients want treated, rather than those that physicians believe should be treated. In a society where attitudes to cannabis use are changing and cannabis is becoming more widely available, CUD may become more prevalent, but providing an ability to completely abstain may, or may not, be the only or most commercially viable response.

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Animal Models of Cannabis Use Disorder

8

Zuzana Justinova

Abbreviations

2-AG	2-Arachidonoylglycerol
α7nACh	Nicotinic acetylcholine receptor type alpha-7
A_{2A}	Adenosine receptor type A2A
AM4040	Anandamide transport inhibitor
VDM11	Anandamide transport inhibitor
CUD	Cannabis use disorder
CB_1	Cannabinoid receptor type 1
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (2013)
FAAH	Fatty acid amide hydrolase
GABA	Gamma-aminobutyric acid
THC	Δ^9-Tetrahydrocannabinol
CP 55,940	A synthetic CB_1 agonist
WIN 55,212	A synthetic CB_1 agonist

Introduction

Cannabinoids are currently one of the most frequently abused class of drugs in the United States [1]. Preparations from *Cannabis sativa* plant (like marijuana and hashish) have historically been most popular among cannabinoid users, but use of synthetic cannabinoids (marketed as "Spice" or "K2") has increased in recent years [2, 3]. Cannabis use will be the focus of this chapter, although it is becoming clear that – similarly to cannabis – chronic use of synthetic cannabinoids also leads to serious adverse consequences that are described in DSM-5 [4] as cannabis use disorder (CUD). CUD is now recognized as a chronic disorder characterized by repeated quit attempts followed by relapse to drug taking that shares similarities with other substance use disorders (SUDs) like tolerance and physical dependence characterized by a withdrawal syndrome upon discontinuation of use [5]. There are high rates of comorbidity between heavy cannabis use and psychotic, affective, anxiety, personality, and bipolar disorders, as well as other SUDs [6, 7], but causal relationships have not been conclusively established. As with other drugs of abuse [8], most cannabis users can likely control or discontinue their use without the aid of psycho- or pharmacotherapy. However, many individuals have difficulty controlling their cannabis use, and 663 thousand people were seeking treatment in the United States in 2016 [9], ranking third after alcohol and prescription pain relievers. It is likely that spreading legalization of recreational use together with increasing availability of high-potency vs. traditional cannabis strains will lead to even greater number of individuals seeking treatment. There are several psychotherapeutic approaches available for patients with CUD with moderate success rates, but no effective pharmacotherapies are specifically approved for treating CUD [10, 11].

In humans, the effects of cannabinoids are complex with highly variable combinations of depressant and stimulant effects depending on the type of the cannabinoid, route of administration, dose, environment, and user's expectations and use history (first time vs. chronic) [7]. Huestis et al. [12] clearly showed in healthy cannabis users that the intoxicant effects are mediated by cannabinoid CB_1 receptors. In rodents, administration of cannabis or its major psychoactive ingredient, Δ^9-tetrahydrocannabinol (THC), produces four characteristic symptoms known as the tetrad (analgesia, hypothermia, hypoactivity, and catalepsy) [13] with underlying CB_1-related mechanisms. In monkeys, disruption of directed behavior and static ataxia has been observed [14]. Moreover, anxiety, cognitive impairment, and cardiovascular changes can also be observed and studied in animals after the administration of cannabinoids [15]. Cannabis produces clear subjective motivational responses in humans, leading to drug-seeking and drug-taking behavior [16]. Different animal models can be used to study the consequences of chronic exposure to cannabinoids. Tolerance and withdrawal syndromes provide only a

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partial correlate of their addictive properties. The motivational properties of cannabinoids related to reinforcement can be evaluated using several behavioral models like drug self-administration, place-conditioning, and drug-discrimination paradigms. Self-administration and place-conditioning models can be modified to study relapse (reinstatement of drug-seeking behavior models). There are also models that can capture other effects of cannabinoids (tetrad, cognitive impairment). The purpose of this chapter is to review animal models that are used to study abuse-relevant effects of cannabinoids and potential medications for the treatment of CUD.

The Rationale for Using Animal Models

Studies in humans must ultimately confirm any theory of cannabinoid reward or effectiveness of any treatment for CUD, but there are advantages to performing basic research in animals. It is clear that no single animal model can capture all aspects and stages of CUD (reward, conditioning, acquisition, maintenance, withdrawal, craving, relapse) and potential treatments become valuable only if they are effective in several models [17]. Animal models can provide certain kinds of information that are difficult or impossible to obtain by studying humans. Studying brain mechanisms that underlie addictive behavior requires use of experimental drugs or procedures that cannot be safely used in humans. When studying behavior, the experience and drug history of human research subjects show high interindividual variability, while high degree of experimental control can be achieved by carefully controlling animals' living environment and exposure to drugs. This allows formulation of clear conclusions regarding causality of observed effects. It is obvious that there are many differences between the brain of humans and nonhuman primates or rodents, but there are also many commonalities, and often the processes occurring in human drug users are corresponding to those in laboratory animals. For example, the general phenomenon of positive reinforcement is common to humans and animals, and similar brain circuitry is involved in humans, monkeys, and rodents [18]. The goals of the animal research are to increase our understanding of the neurobiology underlying the effects of cannabinoids and identify new targets for treatments that can help decrease or stop cannabis use, alleviate withdrawal symptoms, and most importantly prevent craving and relapse to drug taking.

Self-Administration of Cannabinoids and Reinstatement Procedures

Drug self-administration procedures have long been considered the "gold standard" of animal models of drug abuse, because they provide the most direct evidence of rewarding effects of a drug [19]. This procedure shows a high degree of correspondence with human drug abuse by modeling the contingencies that critically influence drug-seeking behavior in animals. Typically, animals are required to perform a simple action (lever press or nose poke) to obtain a drug. The basic procedure can be modified to model many aspects of addiction, e.g., acquisition or maintenance of drug-taking behavior, maintenance of behavior by drug-associated environmental cues, or how relapse to drug use is triggered after a period of abstinence. Drug self-administration in animals is considered a reliable predictor of a drug's potential rewarding effects in humans, because animals will self-administer most drugs that are addictive to humans including opioids, psychostimulants, alcohol, and sedatives [20–22]. However, cannabinoids were an exception to this situation for a long time.

As noted before, the basic functions of the central nervous system in rodents and nonhuman primates are similar enough to humans to serve as useful models of human behavior and physiology. However, regarding the rewarding effect of cannabinoids, there are differences between rodents and primates that are more striking than with other drugs of abuse. Rats learn to self-administer most of the drugs abused by humans, but they do not reliably self-administer THC [23–25]. We do not yet know the exact reasons for this difference, but place conditioning studies suggest that rodents more often perceive THC as aversive rather than rewarding [26]. Nonetheless, rodents have played an important role in cannabinoid research because they self-administer the synthetic cannabinoid WIN 55,212 [27–30]. They also display other abuse-related effects of THC and other cannabinoids that are experimentally accessible and relevant to human CUD (e.g., "tetrad" signs; withdrawal symptoms; subjective effects; cognitive impairment). Regarding self-administration in nonhuman primates, there were many unsuccessful attempts to establish THC self-administration procedures in rhesus monkeys [31–33], which are reviewed elsewhere [34–36]. The only nonhuman primate species that reliably self-administers THC and endocannabinoids (anandamide, 2-AG) is the squirrel monkey [37–39]. This first nonhuman primate model of human cannabis use has been developed by Dr. Steven Goldberg and his colleagues at the National Institute on Drug Abuse [40]. The details on how the procedure was established are the focus of several review articles [34, 41, 42]. The reasons why squirrel monkeys might be particularly sensitive to the cannabinoid reward remain to be determined, but it is possible that they are not as sensitive to the aversive effects of cannabinoids as are other species.

Intravenous Cannabinoid Self-Administration in Squirrel Monkeys

In the basic THC self-administration procedure, the monkeys are seated in a chair in front of a panel that has a lever

and an array of colored cue lights. The sessions last typically 1 h and start with a white house light being turned off and a green cue light turned on to signal availability of the drug. Pressing the lever causes a rapid intravenous delivery of a small amount of clear THC solution through a chronic catheter and changes the green light to amber for 2 s. This schedule of reinforcement is called a fixed-ratio schedule (FR), and the monkeys slowly progress from an initial requirement of one lever press (FR1) to final requirement of ten presses (FR10). Each THC delivery is followed by a time-out period of 60 s during which lever presses have no programmed consequences and all lights are extinguished. The time-out period allows for the drug injection to take effect before the next injection is available. When the time-out elapses, the green cue light is presented again to signal that the next injection is available. It is important that early in the training, the animals are exposed to various THC doses (1–8 μg/kg/injection) and experience extinction periods during which vehicle is substituted for THC to encourage sensitivity to changes in dose. Procedures that have been used with THC self-administration in squirrel monkeys include acquisition, maintenance tests, second-order schedules, and drug-induced and cue-induced reinstatement.

Acquisition of THC self-administration in the initial study [40] was achieved in monkeys with previous experience of self-administering cocaine. The subsequent study in drug-naïve animals showed that the cocaine experience is not essential, because naïve monkeys also readily learned to self-administer THC [38]. The systematic study of the factors affecting acquisition of THC self-administration has not been conducted in monkeys. It has been studied in rats with WIN 55,212, and genetics, as well as sex and gonadal hormones, play a major role. The studies showed that some rat strains (e.g., Long-Evans, Lister Hooded) acquire WIN 55,212 self-administration at higher rates than others (Sprague-Dawley), and intact female rats acquire the behavior more readily than males or ovariectomized females [43–45]. Self-administration of other cannabinoids has also been demonstrated in squirrel monkeys. The endocannabinoid anandamide and its stable analog methanamide are reinforcing under the FR schedule [37]. The endocannabinoid 2-AG was shown to be self-administered by squirrel monkeys previously taking either anandamide or nicotine [39]. Anandamide self-administration was used to study abuse liability of inhibitors of anandamide transport or anandamide metabolism via fatty acid amide hydrolase (FAAH) [46–48].

Maintenance of cannabinoid self-administration involves establishment of a stable baseline level of self-administration. Once the monkeys are well-trained under the FR10 conditions, the requirements for obtaining the drug can be manipulated to study different aspects of addictive behavior or the effects of experimental treatments can be evaluated [1]. The dose dependency of the drug effect can be studied by varying the amount of drug delivered in each injection, which results in construction of a dose-response function [2]. The "cost" of the drug can be manipulated by varying the number of responses required to obtain the drug [3]. The interval between each injection can be manipulated to study anticipation and value of the reward [4]. Different drug can be substituted for the training drug to study potential abuse liability of the substituted drug [5]. A potentially therapeutic drug can be given prior to the sessions to determine whether it decreases self-administration of the training drug. When testing a potential therapeutic, all aspects of the baseline and test sessions are held constant (schedule, cues, drug delivery, presession injection), except for the treatment. Baseline behavior after the vehicle treatment is recorded for at least a week, and then the treatment is given for one to five consecutive sessions, followed by a return to baseline. The process is typically repeated with several doses of the treatment drug. This within-subject, repeated measure design minimizes number of monkeys used for testing. This procedure can detect whether the treatment decreases ongoing cannabinoid use and determine the consistency of the effect over time (immediate effect vs. building over time) and whether or not tolerance develops with extended treatment. However, by examining the effect of the treatment against only one dose of cannabinoid (e.g., dose maintaining the maximum rates of responding), it cannot be ascertained whether the treatment-induced changes in responding represent an increase or decrease in the effectiveness of the self-administered cannabinoid. Thus, it is important to compare dose-response functions of the self-administered cannabinoid with and without treatment. The dose-response functions for cannabinoid self-administration in monkeys have inverted U shapes like with other addictive drugs [37–39]. The nature of the treatment's effect can only be interpreted by determining how it shifts the dose-response function of the cannabinoid [49, 50] (Fig. 8.1).

Second-order schedules of THC self-administration in monkeys [51] can be used to focus on drug-seeking behavior, as opposed to drug taking modeled by fixed-ratio schedules [52, 53]. In humans, cues in the environment related to drug use acquire signaling and rewarding effects of their own over time, and they can guide and reinforce the chain of behavior required to obtain, prepare, and ingest a drug of abuse. Second-order schedules thus allow to study the conditioned reinforcing effects of THC-associated cues. In squirrel monkeys [51], the procedure requires, for example, that animals press a lever under a fixed-ratio requirement that produces brief (2-s) presentations of a cue light for every tenth response (FR10). When a 30-min fixed-interval elapses, the next completed FR produces intravenous delivery of ten injections of THC paired with cue light presentation. Thus, all THC is delivered at the end of the session. The responding during the session is not

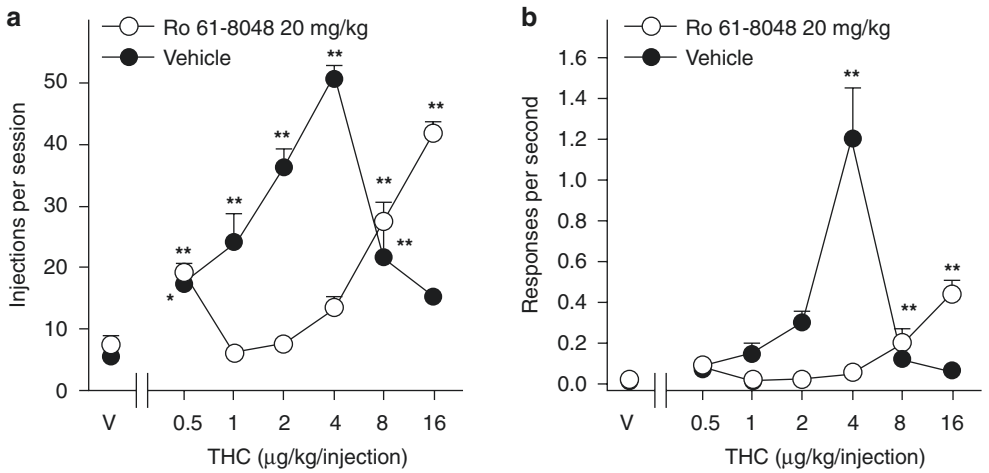

Fig. 8.1 Effects of treatment with Ro 61-8048 on THC self-administration dose-response functions in squirrel monkeys. Ro 61-8048 increases endogenous levels of kynurenic acid, which acts as a negative allosteric modulator of α7nACh receptors. Number of THC injections per session (**a**) and overall response rates in the presence of the green light signaling THC availability (**b**) are shown as a function of the THC dose. Each data point represents the mean ± s.e.m. of the last three sessions under each THC condition and under vehicle conditions ($n = 5$ monkeys). Pretreatment with Ro 61-8048 (20 mg per kg) caused significant downward and rightward shifts of the THC dose-response curves (compared to vehicle pretreatment), which is consistent with a decrease in THC's rewarding effects. The asterisks indicate statistically significant differences versus respective vehicle ("V") conditions (*$p < 0.05$, **$p < 0.01$). (Figure adapted from Justinova et al. [49])

directly influenced by the pharmacological effects of THC and can be described specifically as THC seeking. This drug seeking is maintained at high rates because it produces the brief stimulus that has been consistently associated with THC. Discontinuation of the brief stimuli leads to immediate significant decrease of THC-seeking response. Second-order schedule can be used to evaluate treatments that specifically target cannabinoid-seeking behavior (i.e., motivation to receive the drug) that precedes the drug's self-administration. Treatments that reduce drug seeking might be particularly effective in achieving and maintaining abstinence. Second-order schedule can also be used to study relapse precipitated by drug-associated cues or exposure to drugs.

Drug-induced reinstatement and *cue-induced reinstatement* procedures are used to model relapse, which is one of the main obstacles to the successful treatment of SUDs, including CUD [54, 55]. In humans, relapse can be triggered by re-exposure to the abused drug, to environmental cues associated with the drug use, or stress (not yet studied with cannabinoids in monkeys). Extinction (discontinuation of drug availability) is used to impose abstinence in both the drug-induced and cue-induced reinstatement procedures used with squirrel monkeys under fixed-ratio or second-order schedules. Voluntary abstinence models that were developed recently in rats have not yet been used to study relapse with cannabinoids in monkeys or rats [56]. The imposed (or forced) abstinence causes drug seeking to decrease to very low levels, at which point monkeys can be given injection of THC or another drug at the beginning of the session to evaluate if it increases the drug-seeking responding [46]. Cues that were previously associated with cannabinoid delivery can also be used to induce drug seeking [49]. However, the two procedures differ in how the extinction conditions are set up under an FR schedule of THC self-administration. When imposing abstinence prior to a *drug*-induced reinstatement test, vehicle is substituted for THC, and the cues signaling availability of an injection and brief stimuli paired with drug delivery remain unchanged. Animals still experience the interoceptive stimuli associated with intravenous infusion. In contrast, when imposing abstinence prior to a *cue*-induced reinstatement test, responding does not produce any injections or brief stimuli. After achieving extinction over several sessions, reinstatement test can be conducted. For drug-induced reinstatement, the monkey is given a priming intravenous injection of THC prior to the test session, which typically causes lever responding to increase substantially. For cue-induced reinstatement, the normal cues are presented and responding produces vehicle injections during the session (but no THC injection is given before the test). Re-exposure to the THC-associated cues typically causes a relapse-like increase in the drug-seeking responding. The extinction and reinstatement procedures under the second-order schedule vary from the described methodology and are described in detail elsewhere [51, 53]. Potential medications for treatment of CUD can be given before the reinstatement session to evaluate whether they will prevent the effects of drug or cue re-exposure on drug seeking. Test drugs can also be given alone as priming injections to see whether they can induce drug seeking and thus have a liability to induce relapse.

There are several *pharmacological targets for potential medications* that have been studied using nonhuman primate procedures described above. These are examples of studies that have identified pharmacologic strategies that could lead

to treatments for CUD. The involvement of cannabinoid CB_1 receptors has been probed by using cannabinoid CB_1 antagonists (inverse and neutral). The CB_1 antagonists block THC self-administration under both fixed-ratio and second-order schedules, block reinforcing effects of endocannabinoids (anandamide and 2-AG), and decrease drug-induced and cue-induced reinstatement of cannabinoid seeking in squirrel monkeys [37, 39, 40, 51, 57]. THC self-administration procedures have also been applied to investigate drugs that affect opioid, adenosine, and acetylcholine receptors. Naltrexone (opioid μ1 receptor antagonist) decreases THC taking and seeking in monkeys [51, 58]. Studies with adenosine A_{2A} receptor antagonists show that selective antagonism at presynaptic A_{2A} receptors can block reinforcing effects of THC, while selective antagonism of postsynaptic receptors produces the opposite effect [50, 59]. The first findings on the involvement of the alpha-7 nicotinic acetylcholine receptors (α7nAChRs) in motivational and subjective effects of THC were done in rats [60]. The orthosteric antagonists of α7nAChRs (like methyllycaconitine) have adverse side effects; thus, an indirect approach to increase endogenous levels of kynurenic acid by blocking its metabolism was used in further studies in primate and rodent cannabinoid models [49]. Kynurenic acid acts as a negative allosteric modulator of α7nAChRs, and increasing its levels blocks THC self-administration (Fig. 8.1), cue- and drug-induced reinstatement of THC seeking in monkeys, as well as similar cannabinoid effects in rats, including dopamine elevations in the nucleus accumbens. The monkey self-administration models were also used for studying abuse liability of drugs that inhibit transport or metabolism of anandamide (FAAH inhibitors) [46–48, 61]. Findings show that transport inhibitors (e.g., AM404, VDM11) have robust reinforcing effects, while FAAH inhibitors range from having no reinforcing effects to being effective reinforcers. FAAH inhibitors also differ with respect to their potential for memory impairment [62], and they should be evaluated individually for specific therapeutic and adverse effects.

Intravenous Cannabinoid Self-Administration in Rodents

Most of the studies in rodents have involved intravenous self-administration of the synthetic cannabinoid CB_1 receptor agonist WIN 55,212. The first demonstrations of WIN 55,212 self-administration were done under very specific conditions in restrained mice [29, 63]. This procedure was then extended to freely moving rats self-administering over multiple sessions, which allowed study of the acquisition of the behavior, its maintenance, and its extinction upon discontinuation of the drug delivery [27]. This procedure in rodents has been perfected in recent years to investigate different variables (strain, sex, doses), relapse, and treatment drugs [28, 30, 43–45, 49, 64]. WIN 55,212 self-administration in rodents tends to be more sensitive to training conditions and genetic background of the subjects than self-administration of cocaine or heroin. Sprague-Dawley rats that reliably self-administer heroin or cocaine do not always self-administer WIN 55,212, while Long-Evans or Lister Hooded rats do so more consistently [43, 44, 65]. It is not clear how useful this rodent model is for predicting the abuse potential of other cannabinoids, since THC is not self-administered by rats previously trained to self-administer WIN 55,212 [28]. The synthetic cannabinoids differ from THC in their efficacy and binding affinity at cannabinoid receptors, as well as activation of second-messenger systems, and thus, the results obtained with them might not generalize to THC. Other cannabinoids (like JWH-018 or 2-AG) are also self-administered by rodents, albeit at lower rates than observed with WIN 55,212 [66, 67]. The rodent reinstatement models of relapse to cannabinoid seeking have been developed and used to study sex and strain differences or treatment effects [45, 49, 68–70]. WIN 55,212 priming injections or the cues reinstate more robust drug seeking in intact females than males or ovariectomized females.

Craving is a subjective state defined as a strong desire or urge to use cannabis and it is among the diagnostic criteria for CUD (DSM-5). Craving is induced by withdrawal from chronic use; it increases during early abstinence and remains elevated for extended time periods (see review by [56]). Exposure to drug-related cues can motivate the individual to seek the drug and precipitate relapse. Craving is, however, difficult to address experimentally in animals. Drug seeking induced in reinstatement models by drug-related cues or contexts represents in part the cue-elicited craving observed in humans. A variation of the reinstatement procedure has been used in "incubation of drug craving" studies in which subjects are tested under extinction conditions on different abstinence days [71]. Incubation of drug craving refers to the time-dependent increases in cue-induced drug seeking after cessation of drug taking [72]. This phenomenon has been established with non-cannabinoid drugs of abuse like methamphetamine, cocaine, and nicotine (see [56] and only recently with cannabinoids [65]. In this study, rats exhibited significant increase in cue-induced reinstatement of WIN 55,212 seeking after 21 days of abstinence. Similar to study with methamphetamine [73], incubation of craving procedure could be employed in screening of candidate treatments for CUD.

Other Animal Models of Cannabinoid Reward and Abuse-Related Effects

Drug self-administration procedures are considered the most valid and flexible models that provide a direct behavioral measure of cannabinoid reward. However, there are

other indirect behavioral measures that provide valuable information about cannabinoid reinforcement and other abuse-related effects. Procedures like place conditioning, drug discrimination, and intracranial techniques (microinjection, microdialysis, and electrical self-stimulation) are widely used in rodents. Other procedures like withdrawal studies, tetrad test, and models evaluating cognitive performance will also be briefly described below. Together, these approaches have allowed accumulation of a large body of knowledge on cannabinoids and identification of medication targets for CUD.

Indirect Behavioral Measures of Reward

Place-conditioning procedure utilizes Pavlovian conditioning processes and provides a relatively simple means of assessing the rewarding effects of cannabinoids in rodents [26]. During training, the effects of a cannabinoid are associated with one of two distinct compartments of an apparatus, while vehicle is associated with the other compartment. The animals receive the drug (e.g., THC) by systemic injection prior to the session and are not required to make any operant responses. After the effects of THC and vehicle have been paired with their respective compartments several times, a test is performed during which the rat is given access to both compartments and the relative amount of time spent in each compartment is measured. If the animal spends more time in the THC-paired compartment (i.e., exhibits a *conditioned place preference*), it implies that the drug has a rewarding effect that was transferred to the environmental stimuli of the drug-paired compartment. The procedure can also detect aversive effects of the drug, which are inferred if the rat avoids the drug-paired compartment and spends more time in the vehicle-paired compartment (i.e. exhibits *conditioned place aversion*). In most studies with cannabinoid agonists, rats have shown either conditioned place aversion or no clear preference for either compartment [74–79]. In case of THC, some evidence suggests that low doses can be rewarding, but higher doses tend to have aversive effects [80]. The failure of THC to consistently induce place preferences in rats can be a result of its concurrently occurring aversive effects (like anxiety) masking its rewarding properties. Some argue that aversive effects of cannabinoids can be attenuated by prior cannabinoid exposure in adolescent rats [81, 82], but the results are not consistent [83]. Place conditioning can also be used for reinstatement studies [84], but these tests have not been performed with cannabinoids.

Drug discrimination procedures provide a means of assessing the interoceptive effects of drugs, which are considered analogous to the subjective effects perceived by humans after drug administration [85–87]. In a typical procedure, animals (usually rats but also mice and nonhuman primates) are trained to detect the effects of a cannabinoid drug from a vehicle (or another drug). Rats are trained in an operant chamber with two levers and injected with a treatment prior to the session. When they receive an injection of THC, responding on one lever produces delivery of food pellets. When the vehicle is injected, responding on the opposite lever produces food. Each lever is consistently paired only with one type of treatment that signals which lever produces food on that particular day. After extensive training, rats learn to respond very reliably on the appropriate lever during training sessions. Once rats reach selected accuracy criteria, tests can be conducted to determine whether a drug produces subjective effects similar to those of THC or whether a drug blocks or enhances the effects of THC, which is valuable when screening novel compounds or candidate medications. Training rats to reliably detect the subjective effects of THC requires a considerable amount of time (several months), but well-trained rats can be tested repeatedly, which is ideal for screening large number of novel compounds. It is difficult to determine what property of the drug effect the rat is responsive to as the interoceptive effects of drugs have several different components. Drug discrimination does not directly measure reinforcement, but some of the interoceptive effects of THC perceived by animals are presumably similar to subjective effects such as "high" in humans. Thus, when a tested drug generalizes to THC, it can be inferred that it produces interoceptive effects similar to THC and could also have similar abuse liability or adverse effects. Drug discrimination is highly pharmacologically specific, which means that drugs that do not activate CB_1 receptors do not generalize to THC [88–91]. THC-like discriminative-stimulus effects are produced by partial or full agonist at CB_1 receptors like anandamide, methanamide, and synthetic CB_1 agonists found in "Spice" drug preparations [92–96].

Intracranial Techniques

Intracranial microinjection techniques can be used to deliver cannabinoids in a modified self-administration procedure or deliver drugs during or prior to other procedures (drug discrimination, place preference, etc.). Using these approaches allows researchers to map the brain areas where the drug has rewarding effects or study interactions between cannabinoids and other drugs [97]. In the self-administration procedure, the animal obtains the drug by performing a behavioral response (e.g., lever press), and the drug is delivered directly into specific brain site via an implanted cannula. Rats will intracerebroventricularly self-administer CB_1 agonists THC and CP 55,940 [98, 99]. They will also self-administer THC and anandamide into the ventral tegmental area and the shell of the nucleus accumbens [100], which are critical areas of the brain's reward circuitry and sites of action of other abuse

drugs like psychostimulants and opioids. Further testing with microinjections of THC in combination with place conditioning indicated that THC had reinforcing effects only in the posterior parts of the ventral tegmental area and the shell of nucleus accumbens [100]. These findings support the conclusion that cannabinoids produce rewarding effects through essentially the same reward-related brain circuitry as other drugs of abuse. In another study, the microinjection technique was used to deliver beta-endorphin into the ventral tegmental area, which resulted in potentiation of the discriminative-stimulus effects of THC in rats [101]. A potential drawback of the intracranial microinjection techniques can be that injecting cannabinoids (or test drugs) directly into discrete areas might produce concentrations of the drug that are not reached when the drug is administered systemically. Moreover, isolating a selected area of the brain might not be representative of the effects that occur when cannabinoids are distributed throughout the brain. The results obtained with these techniques should be considered along with the results from other models.

Microdialysis procedures allow sampling of fluid from discrete brain regions to measure extracellular levels of neurotransmitters and other neurochemicals [102] and can be combined with behavioral techniques like self-administration [64, 103]. The sampled fluid can be analyzed for levels of several molecules, but the timescale resolution is in minutes. Reward-related microdialysis research with cannabinoids has focused on mesolimbic dopaminergic pathways, mainly the ventral tegmental area and nucleus accumbens in rodents. Cannabinoid agonists have effects on these areas that are comparable to those produced by all other drugs of abuse. For example, systemic treatment with THC, anandamide, 2-AG, or WIN 55,212 causes release of dopamine in the shell of nucleus accumbens [64, 96, 103–105]. Direct microinjection of THC into the ventral tegmental area or nucleus accumbens also causes elevation of dopamine levels in these areas, which suggests that the rewarding effects of cannabinoids are mediated by direct actions on neurons in these areas [106]. Microdialysis is used to assess the release of other neurotransmitters like glutamate and GABA, as well as endogenous cannabinoids. For example, systemic administration of THC decreases extracellular GABA and increases extracellular glutamate and dopamine levels in the rat prefrontal cortex [107]. Drugs of abuse alter levels of endogenous cannabinoids in the brain, but the effects differ after acute vs. chronic exposure and are drug-, dose-, and area-specific [108]. Here are just a few examples. Heroin self-administration causes increase of anandamide levels with concomitant decrease of 2-AG levels in the nucleus accumbens, while cocaine does not change endocannabinoid levels in this area [109]. Nicotine self-administration increases extracellular levels of both anandamide and 2-AG in the rat ventral tegmental area, but noncontingent administration of nicotine does not affect anandamide levels in this area [110]. The fast-scan cyclic voltammetry procedure is similar to microdialysis, but no extracellular fluid is collected, rather it detects the release of one neurotransmitter at a time by measuring electrochemical properties of the molecule with a probe [111]. The main advantage of voltammetry is its subsecond timescale resolution (compared to minutes with microdialysis).

Intracranial self-stimulation (ICSS) is an operant conditioning method used to produce brain stimulation reward via direct stimulation of a specific brain region in an experimental setting. Animals are allowed to press a lever that produces a brief electrical current in a discrete brain area (e.g., mesolimbic dopaminergic system). It is known that such stimulation can have robust rewarding effects and the technique has been used to map the reward systems of the brain [112]. In drug abuse research, application of this technique capitalizes on the ability of drugs to alter the threshold intensity and frequency required for the stimulation to have a reinforcing effect. Drugs of abuse typically facilitate ICSS, which means that they increase activity of dopamine cells in the reward system thus lowering the threshold for the reinforcing effects of the electrical stimulation [113]. There is evidence that cannabinoid CB_1 agonists, like other drugs of abuse, increase sensitivity to electrical brain stimulation (enhanced ICSS) [114–116], while the antagonist/inverse agonist rimonabant can have an opposite effect [117]. This technique can detect changes in the sensitivity of the reward system induced by potential treatments or evaluate how these drugs affect thresholds altered by cannabinoids [79]. The ICSS can also be useful in studying how treatments affect decreases in the activity of reward circuits during withdrawal from chronic cannabinoid exposure, which manifest as increased thresholds for reinforcing effects of electrical stimulation [118]. Taken together, the findings obtained with ICSS, intracranial microinjections, and microdialysis techniques indicate that cannabinoid agonists affect the reward circuitry of the rodent brain in a manner consistent with those of other drugs of abuse and can be valuable for medication screening.

Other Behavioral Techniques

Discontinuation of heavy, chronic cannabis use can lead to occurrence of withdrawal symptoms [119, 120]. After years of debate, DSM-5 included cannabis withdrawal syndrome as one of the diagnostic criteria for CUD. The diagnostic criteria for cannabis withdrawal include symptoms such as irritability, anxiety, sleep disturbances, decreased appetite, and depressed mood. These symptoms are not as severe as those associated with opioid or ethanol withdrawal, but aversive enough that many users report using marijuana to alleviate withdrawal symptoms [121]. Persistent chronic cannabis use

is often perpetuated by avoidance of withdrawal symptoms, and medications that could relieve these symptoms might be helpful in achieving abstinence.

Cannabinoid withdrawal procedures have been used in animals to model the effects of discontinuing chronic marijuana use and typically involve passive noncontingent exposure to THC as opposed to self-administration. In rodents, the behavioral effects induced by simply discontinuing THC exposure (a procedure known as spontaneous withdrawal) are subtle and can be hard to detect. This is likely due to slow elimination of lipophilic compounds like THC from the body [122], although more prominent withdrawal effects have been reported with the full-agonist cannabinoid WIN 55,212 [123]. Thus, many studies have used precipitated withdrawal procedures, in which administration of a cannabinoid CB_1 antagonist (e.g., rimonabant) causes an abrupt reversal of THC's effects [124–126]. Precipitated withdrawal produces symptoms (scratching, face rubbing, licking, wet dog shakes, ataxia, myoclonic spasms) that are similar to those observed after spontaneous withdrawal but occur at higher rates and in a higher percentage of rodents. In monkeys, spontaneous withdrawal from THC has been observed and can produce an increase in locomotion and aggressiveness [127]. Withdrawal precipitated by rimonabant manifests as head shaking and tachycardia in THC-treated rhesus monkeys [128]. Sensitive behavioral procedures have also been developed to detect effects of THC withdrawal by measuring disruptions of learned behavior, such as food-reinforced lever pressing [129, 130]. In rhesus monkeys, drug discrimination has been used to model mild cannabis withdrawal by training monkey to discriminate between a dose of THC with vs. without rimonabant [131]. In this study, rimonabant did not reverse the effects of WIN 55,212 suggesting that non-CB_1 effects are relevant to the subjective effects of WIN 55,212 and possibly other synthetic cannabinoids. Since the withdrawal signs are not observed in THC-naïve control animals, the withdrawal symptoms are a consequence of development of tolerance and neuroadaptations caused by chronic cannabinoid exposure. In this regard, withdrawal studies offer means for uncovering the underlying physiological processes that are altered by chronic cannabinoid use. Precipitated withdrawal procedures are also highly relevant to the possible clinical use of cannabinoid antagonists, which have been suggested as a treatment for CUD.

The tetrad test is used to screen for cannabinoid-like activity of novel compounds in rodents [132, 133]. The four effects measured in this test are suppression of spontaneous locomotor activity, reduced pain perception, hypothermia, and catalepsy, and these effects are shared by most cannabinoid agonists. Catalepsy and locomotor suppression represent effects that might act to limit intake of self-administered cannabinoids. Reduced pain perception (hypoalgesia) represents a potentially beneficial effect of medical marijuana and other cannabinoids, and there have been substantial efforts to develop cannabinoid-based pain medications. As with opioids, there are concerns about potential abuse leading to dependence, but novel approaches to designing compounds (e.g., allosteric modulators, biased ligands) could yield cannabinoid therapeutics without unwanted adverse effects [134, 135].

Models of cognitive impairment can be used for detection of the adverse effects of cannabinoids on several types of cognitive function (memory, learning, attention) [136]. They can also aid efforts to develop cannabinergic drugs that retain medicinal value with lesser adverse effects on cognition or evaluate medications for their ability to reverse or exacerbate adverse effects of cannabinoids [49, 62]. There are many tests available for evaluation of different aspects of cognition that cannot be reviewed in detail here, but modern technologies (like touchscreens) provide flexible means to administer a variety of complex behavioral tasks before, during, and after drug administration [137]. A recent study used a battery of touchscreen-based assays to compare effects of different cannabinoid drugs in squirrel monkeys [138]. The study assayed different facets of cognition-related behavior by measuring learning (repeated acquisition), cognitive flexibility (discrimination reversal), short-term memory (delayed matching-to-sample), and attention (psychomotor vigilance). In these tests, THC produced dose-related decrements in the performance of each task, which were reversed by rimonabant. On the other hand, anandamide or its metabolically stable analog methanandamide had much less pronounced detrimental effects on performance in these assays. Comparing different ligands can detect differences in the activation of CB_1 receptors and can point to therapeutics with fewer deleterious effects on cognitive performance.

Conclusion

Animal research produced most of what we know about cannabinoid reward and abuse-related effects, but much remains to be learned. This chapter aimed to highlight animal models that are used to advance our understanding of the endocannabinoid system and for the screening and evaluation of medications for treating CUD. With cannabis legalization underway in the United States, larger numbers of people are being exposed to cannabis and the incidence of cannabis dependence is increasing. The need to develop viable treatments is clear as there are no medications specifically approved for the treatment of CUD. Preclinical research is an important early step in any pharmacotherapy development effort, and many of the aspects of drug addiction can be studied by using specific animal models. The self-administration paradigm provides the most direct evidence of a drug's reinforcing effects, and nonhuman primate and rodent models were developed with cannabinoids. THC self-administration in squirrel monkeys, together with other paradigms in

rodents (e.g., drug discrimination, intracranial techniques), has been used in testing of several pharmacological approaches for modifying the reinforcing/subjective effects of THC, but translational value of these animal models is yet to be demonstrated for CUD. Research using addiction-related animal models is indeed indispensable for developing safe new medications, as well as for evaluating interactions between cannabinoids and other drugs. Improving and combining the existing models in complementary ways should lead to development of treatments that will help people struggling with CUD without harmful side effects.

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Human Laboratory Models of Cannabis Use Disorder

9

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Introduction

Over the past ~20 years, there have been substantial changes in cannabis use and related public policy in the United States. Eight states (AK, CA, CO, MA, ME, NV, OR, WA) and the District of Columbia have passed legislation legalizing cannabis for recreational use [84], and five of these states currently have state-sanctioned recreational cannabis dispensaries in operation (AK, CO, OR, NV, and WA). An additional 22 states have legalized medicinal use of cannabis products containing psychoactive levels of tetrahydrocannabinol (THC) for individuals with qualifying medical conditions, including chronic pain, multiple sclerosis, and epilepsy [21, 47, 66, 90], and 13 other states now permit medical access to products containing another cannabinoid, cannabidiol. Only three states (ND, NE, ID) completely prohibit cannabis and cannabinoids. Despite the changing legality in individual states, cannabis remains illegal under the federal law. It is currently classified as a Schedule 1 substance under the Controlled Substances Act of 1970, a classification that indicates a high potential for abuse and no currently accepted use in medical treatment. Thus, there is currently a fundamental disconnect between state and federal cannabis laws for the vast majority of the United States, and the implications of these state-level changes on CUD, and public health in general, are just beginning to be borne out.

Although a myriad of complexities preclude definitive causal inference at this time, state-level policy changes that reduce restrictions on access to cannabis products are paralleled by increases in the prevalence of cannabis use [41]. Although most individuals who use cannabis never develop clinically significant problems with their use of cannabis, a subset develop patterns of chronic, heavy use, which can be associated with impairments in memory, temporal and spatial perception [3], decreased academic performance, and potentially deleterious effects on adolescent brain development [90]. Further, CUD develops in at least 50% of daily or near-daily heavy users [12], with symptoms of withdrawal occurring in up to one-third of these users in the general population, and up to 95% of heavy users who enroll in either human laboratory studies, clinical trials, or community-based treatments for CUD [41]. Cannabis as the primary substance of abuse accounted for 14% of admissions to publicly funded substance abuse treatment programs in 2015 in the overall population, third to heroin and alcohol. Cannabis was also the primary substance for which treatment was sought for those aged 12–17 years old [16]. States with less restrictive cannabis laws have seen the largest increases in cannabis use in adults, although comparable increases have not been observed in adolescents [44]. Overall, the growing acceptance of cannabis and increases in both medical and recreational cannabis use [44] highlight the importance of carefully controlled studies defining the factors that maintain problematic cannabis use, with the ultimate goal of providing data that can both improve the treatment of CUD and inform cannabis-related public policy.

Human Laboratory Models for Studying CUD

Human laboratory studies have a long and rich history as powerful tools for increasing our scientific understanding of psychoactive drug use, including factors underlying the development of problematic use behavior, and mechanisms through which substance use disorders can be treated [5, 6, 24, 26, 30, 31, 54, 78, 80, 81]. More specifically, human laboratory models and procedures have been developed to examine discrete components of CUD, including intoxication, positive reinforcing effects, abstinence initiation, tolerance, negative reinforcing effects, and relapse.

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Intoxication To measure acute cannabis intoxication in the laboratory setting, participants are experimentally administered a precise amount of smoked cannabis with a specific concentration of THC using a paced puffing procedure [23], controlling the duration of inhalation and time spent holding smoke in the lungs. Participants complete abuse-related self-report measures such as ratings of cannabis "liking" and "good effect" before and at precise timepoints after cannabis administration. Thus, this methodology allows for a timeline of subjective effects of THC on mood and feelings of intoxication following precise doses of drug.

Positive Reinforcing Effects Initial research on the behavioral pharmacology of cannabis sought to develop a reliable laboratory measure of its positive reinforcing effects [17, 29, 70, 91]. Non-treatment-seeking cannabis smokers were presented with a series of discrete choices between self-administering cannabis with various levels of THC and receiving non-drug alternative reinforcers, including money [91] or a preferred food [29]. These studies demonstrated that cannabis containing THC, the primary psychoactive component of cannabis, was positively reinforcing, i.e., self-administered significantly more than cannabis containing minimal THC, and the choice to self-administer cannabis could be shifted as a function of a monetary alternative.

Tolerance and Negative Reinforcing Effects Inpatient human laboratory studies have characterized symptoms of tolerance and withdrawal resulting from sustained administration and abrupt discontinuation of smoked cannabis and from oral administration of synthetic THC, i.e., dronabinol [30, 31]. For example, in one model, acute administration of either dronabinol or smoked cannabis initially produced increased ratings of subjective effects indicative of abuse liability (i.e., "high," "good drug effect," "willingness to take again"). However, tolerance to these effects was evident after several continuous days of administration. Notably, tolerance developed following sustained administration of smoked cannabis high in THC, but not for cannabis low in THC. Abstinence from dronabinol and smoked cannabis cigarettes produced reliable, time-dependent increases in ratings of anxiety, depressed mood, and irritability, as well as marked disruptions in sleep and food intake [30, 31]. Thus, abstinence from THC produces a distinct cluster of withdrawal symptoms.

Other groups have demonstrated that abrupt abstinence from frequent, heavy cannabis use results in changes in mood, food intake, and sleep that have temporal and qualitative characteristics of a withdrawal syndrome, using both inpatient and outpatient laboratory procedures [10, 11, 57, 58]. These models have assessed withdrawal using self-report craving assessments like the Marijuana Craving Questionnaire (MCQ) [45], withdrawal symptom checklists such as the Cannabis Withdrawal Scale (CWS) [1], visual analogue mood questionnaires, journal entries, and confirmatory quantitative cannabinoid level testing [13, 87–89]. In some inpatient models, an attempt is made to standardize cannabis exposure prior to a period of controlled experimental abstinence and the measurement of withdrawal. Participants often complete 1–2 days of experimenter-controlled cannabis administration followed by a period abstinence, and subjective measures of mood and sleep quality, objective measures of sleep efficiency and duration, and caloric intake are assessed as signs of withdrawal [37, 58, 88].

In one 16-day outpatient study [10], daily cannabis smokers used cannabis as usual for the first 5 days, followed by 3 days of abstinence, a return to regular use patterns on days 9–13, and concluded with another 3 days of abstinence. During each abstinence phase, significant increases in overall discomfort were observed. Specifically, increased ratings of aggression, anger, cannabis craving, appetite disturbance, irritability, and sleep difficulty were reported during the first period of abstinence, and all notably returned to baseline once cannabis use resumed. During the second phase of abstinence, participants again reported significant cannabis craving, appetite disturbances, and difficulty sleeping [10]. Another outpatient model examined the time course of cannabis withdrawal symptoms: cannabis smokers underwent a 28-day detoxification procedure, where symptoms of withdrawal were assessed on days 1, 3, 7, and 28 of abstinence. In line with other studies, symptoms of withdrawal, including increased provoked aggressive behavior, peaked at day 7 and returned to baseline by day 28 [57].

In a further investigation of the time course of cannabis withdrawal, Budney et al. [11] evaluated heavy cannabis smokers compared to ex-smokers on measures of anxiety, food intake and body weight, irritability, sleep disturbances, and gastrointestinal issues over 50 days [11]. Following 5 days of smoking-as-usual, participants underwent 45 days of abstinence from cannabis. Within 3 days of abstinence, characteristic behavioral changes, along with disturbances in mood, sleep, and appetite, were apparent in those using cannabis daily; these symptoms largely resolved within 21 days, with the exception of strange dreams, which persisted through the end of the study [11].

In an inpatient laboratory study, patients resided on a research unit for approximately 1 month of enforced abstinence and a battery of behavioral and physiological assessments were collected [58]. Ratings of anxiety and craving were highest at admission and steadily declined over time, while sleep disturbances persisted throughout the monitoring period. Overall, withdrawal symptomology resolved in a shorter time course than aforementioned outpatient studies. The authors suggested that the inpatient environment, devoid of many of the cues associated with cannabis use, may have lessened the manifestation and duration of withdrawal symp-

toms; but 66% of patients dropped out by the fourth week, potentially indicating attrition of those with more severe withdrawal symptoms [58].

The human laboratory findings detailed above have been further confirmed by others [85, 87] and are consistent with epidemiological studies and trends of outpatient self-report studies. Using the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) dataset, Hasin et al. [42] reported a significant prevalence of cannabis withdrawal, where 44% of frequent users endorsed symptoms consistent with at least mild withdrawal, including weakness, sleep disturbances, psychomotor retardation, anxiety, and depression. Further, utilizing outpatient self-report, Vandrey and colleagues extrapolated their findings of a cannabis withdrawal syndrome to include a study of adolescents seeking treatment for their cannabis use, where at least 30% of the sample rated their withdrawal symptoms as at least moderate [85].

Thus, cannabis withdrawal is time-dependent, and most symptoms typically resolve within 21 days, mimicking temporal patterns of withdrawal resulting from other drugs such as nicotine [51, 86]. The severity of cannabis withdrawal also appears to be related to severity of use, where heavier users report a higher number of and more severe withdrawal symptoms [8, 61]. Further, cannabis withdrawal is pharmacologically specific: dronabinol attenuates symptoms of cannabis withdrawal at doses that participants could not distinguish from placebo [34]. Given the ample evidence identifying and replicating a distinct cluster of withdrawal symptoms resulting from cannabis abstinence, cannabis withdrawal was added to the DSM-5 [12, 43].

To meet DSM-5 criteria for cannabis withdrawal, participants must demonstrate three or more of the following symptoms following abrupt reduction or cessation of consistent cannabis use: (1) irritability, anger, or aggression, (2) nervousness or anxiety, (3) sleep difficulty (e.g., insomnia, disturbing dreams), (4) decreased appetite or weight loss, (5) restlessness, (6) depressed mood, and (7) at least one of the following physical symptoms causing significant discomfort – abdominal pain, shakiness/tremors, sweating, fever, chills, or headache [4]. Note, the DSM-5 does not include craving as a symptom of cannabis withdrawal, though this symptom is commonly measured in investigations of CUD treatment.

Relapse A laboratory model of relapse has also been developed, with the goal of assessing the factors that influence the decision to self-administer cannabis following a period of abstinence in non-treatment-seeking cannabis smokers. Since it is not ethical to offer cannabis to individuals seeking treatment, relapse is *modeled* in cannabis smokers who are not self-motivated to abstain [35]. Specifically, participants who are abstinent from cannabis for several days are offered the opportunity to self-administer individual puffs of cannabis at a monetary cost, deducted from overall study earnings [27, 37, 35, 46]. The greatest weight is given to the decision to resume cannabis self-administration each day, so the initial puff is the most expensive, with subsequent puffs decreasing in cost, once "relapse" has occurred. A range of costs were tested in a pilot study, and cannabis self-administration was shown to decrease linearly as a function of cost [27]. Analysis of a range of studies shows roughly 50% of daily cannabis smokers choose to "relapse" in this model, and this variability allows to study the individual factors that predict this behavior [37], as well as the effect of medications on the decision to return to cannabis use after a period of brief abstinence (see below). Although the processes that underlie decisions to "relapse" clearly differ between non-treatment seekers and treatment seekers, this difference does not matter if the model has predictive validity, the most important feature of a human laboratory model.

Abstinence Initiation Modeling the factors that influence whether an ongoing cannabis smoker will reduce or cease smoking cannabis is also essential for the development of CUD pharmacotherapy, as few patients seeking treatment for their cannabis use are abstinent at the onset of treatment [7], and initiating abstinence and preventing relapse likely require distinct therapeutic approaches. Since most patients seeking treatment for their cannabis use still actively use cannabis, human laboratory models can be used to determine which environmental condition or medications would shift ongoing patterns of use. One approach is to compare cannabis self-administration in non-abstinent, non-treatment-seeking cannabis smokers during placebo vs. active medication maintenance [39, 38, 40]. Another approach involves examining contingency management procedures (i.e., providing participants with monetary incentives for evidence of cannabis abstinence) as methods to produce high rates of initial abstinence [79]. Contingency management procedures can also increase treatment retention, thus may serve to create a critical window during which treatments that have delayed or relapse prevention-specific effects may be delivered more effectively and with less dropout.

Human Laboratory Models Testing Medications to Treat CUD

A model that reliably captures key features of CUD by assessing the positive subjective and reinforcing effects of cannabis, withdrawal symptoms following abrupt discontinuation of use, abstinence initiation, and a measure of relapse in daily cannabis smokers can be used to assess the effects of potential treatment medications on these discrete behavioral outcomes.

Treatment approaches showing promise in the human laboratory need to be validated by randomized controlled clinical trials before conclusions about clinical efficacy may be drawn. Thus, medication or medication combinations showing promise under the methodological rigor of human laboratory models will often be moved to a clinic setting to be tested in a larger, treatment-seeking sample of substance users. Alternatively, if a medication is unsuccessful under laboratory scrutiny, it typically does not undergo more expensive clinical trial testing. Human laboratory models, thus, provide an essential intermediary step between preclinical models and large clinical trials. The following sections briefly summarize the results of these studies, organized by test medication class. For a more detailed review, see Brezing and Levin [7].

Cannabinoid Receptor Agonists in the Treatment of CUD

Across all medication classes tested in the human laboratory, cannabinoid agonists, or medication combinations including cannabinoid agonists, demonstrate the most promise as potential treatments for CUD. This is consistent with studies examining the efficacy of pharmacotherapies for other substance use disorders; agonist or partial agonist treatment approaches are among the most successful (e.g., methadone and buprenorphine for opioid use disorder (OUD), nicotine replacement therapy or varenicline for tobacco use disorder). The results of human laboratory studies testing orally administered synthetic THC (dronabinol), and the longer-acting synthetic THC analogue, nabilone (Cesamet), are described.

Oral THC (Dronabinol)

Dronabinol has been consistently shown in both human inpatient and outpatient laboratory studies to dose-dependently reduce cannabis withdrawal symptoms while producing significantly lower levels of abuse liability-related subjective effects than smoked cannabis. In an early study, Haney et al. [34] reported that dronabinol decreased cannabis craving, food intake, and mood disturbances without evidence of intoxication in abstinent, non-treatment-seeking cannabis smokers. Two subsequent studies also demonstrated that dronabinol's effects on withdrawal symptoms are dose-dependent and generalize across inpatient and outpatient study conditions [13, 89].

However, dronabinol has not been shown to reduce cannabis self-administration in the human laboratory, either in participants who were abstinent from cannabis [35] or those who were tested under non-abstinent conditions [40]. These laboratory findings are highly consistent with clinical trial data. Levin et al. [62] carried out a clinical trial of dronabinol in treatment-seeking cannabis users. Relative to placebo, dronabinol significantly reduced symptoms of withdrawal (as in the human laboratory) and improved treatment retention, but there was no significant difference in abstinence rates between groups.

Given dronabinol's efficacy at reducing cannabis withdrawal symptoms, a subsequent study tested the hypothesis that combining it with lofexidine, an α2-receptor adrenergic agonist would effectively reduce withdrawal and cannabis self-administration. A series of preclinical studies showed that cannabinoid abstinence produces noradrenergic hyperactivity, and α2-receptor agonists reverse this effect and reverse symptoms of precipitated THC withdrawal, thereby providing the rationale for testing lofexidine (see Haney et al. [35]). As hypothesized, the combination of lofexidine and dronabinol produced robust attenuation of cannabis withdrawal symptoms while also decreasing the laboratory measure of cannabis relapse [35].

Yet the findings of a subsequent clinical trial did not support these promising findings from the human laboratory. Levin et al. [63] found no differences in abstinence rates, withdrawal symptoms, or retention rates in patients receiving combined lofexidine and dronabinol relative to those receiving placebo. The discrepancy between the laboratory and the clinic is at least in part due to poor tolerability of the medication combination in a clinical setting. Forty percent of patients in the active medication condition were unable to tolerate the target lofexidine dose (mostly due to dizziness, fatigue, hypotension), which was *lower* than the dose shown to be effective in the inpatient laboratory.

This study highlighted the importance of devising human laboratory studies that prioritize medication tolerability in an outpatient setting; inpatient studies permit the use of higher medication doses because they allow for continuous monitoring for safety and side effects (e.g., hypotension), which is not feasible in an outpatient clinical treatment setting [63]. Thus, medication tolerability and frequency of administration are critical design considerations to improve the predictive validity of human laboratory models designed to test potentially medications for the treatment of CUD [27].

Nabilone

Nabilone is a synthetic analogue of THC that has shown particular promise in laboratory models of CUD. Nabilone has better bioavailability, a longer duration of action, and lower abuse liability than dronabinol [59, 71], and since it produces unique urinary metabolites, researchers can distinguish cannabis use from medication compliance. Haney et al. [37] investigated two doses of nabilone in the human laboratory and showed that this medication significantly decreased a laboratory measure of cannabis relapse and improved mood

symptoms of withdrawal, such as irritability. Further, the higher nabilone dose also decreased craving for cannabis, increased quality of sleep, and improved food intake [37]. In 2016, Herrmann et al. used a similar human laboratory design to test the combination of nabilone and the $GABA_A$ agonist, zolpidem, hypothesizing that combining nabilone with an efficacious sleep medication may produce more robust reductions in cannabis withdrawal and relapse than those observed with nabilone alone by Haney et al. [37]. Zolpidem was also tested alone, and although it improved sleep during cannabis withdrawal relative to placebo, it did not reduce relapse. The combination of zolpidem and nabilone provided a more comprehensive reduction in withdrawal symptoms (negative mood, anorexia, disrupted sleep) and also reduced cannabis relapse [46]. The authors suggest that the majority of these effects are attributable to nabilone. These laboratory findings await confirmation in clinical treatment settings, but the results of these studies demonstrate that nabilone holds considerable promise for CUD treatment.

Cannabinoid Receptor Antagonists in the Treatment of CUD

Laboratory studies have also examined the efficacy using CB1 receptor antagonists as treatments for CUD. Antagonists have been shown to block the subjective and reinforcing effects of various agonist drugs of abuse, and the efficacy of the opioid antagonist naltrexone for the treatment of OUD indicates that this approach may have promise for CUD. Three placebo-controlled human laboratory studies have tested the effects of the CB1 receptor antagonist, rimonabant, in combination with smoked cannabis [25, 49, 50]. These studies showed that rimonabant significantly reduced the cardiovascular [25] and abuse liability-related subjective effects [49, 50] of smoked cannabis, e.g., feelings of "high," "stoned," and ratings of cannabis "strength." However, while the doses of rimonabant tested in these studies appeared to be well-tolerated by study participants, rimonabant became unavailable for further testing due to a deleterious profile of side effects, including depression and anxiety [72].

Other Candidate Medications for the Treatment of CUD

Cannabidiol

Cannabidiol, a constituent of the cannabis plant, has been receiving considerable attention of late for its potential therapeutic utility, including potential anxiolytic, anticonvulsant, anti-inflammatory, and neuroprotective effects [52, 53, 76]. Cannabidiol has a complex pharmacology. In contrast to THC, cannabidiol has minimal affinity for CB1 and CB2 receptors [74] and produces no intoxication [93]. The effects of cannabidiol in combination with THC have been mixed, with some data suggesting it may reduce THC's mood-altering and cognitive effects [20, 82, 94], while others show no effect [55, 77, 93]. If oral cannabidiol reduces cannabis intoxication, it could be a potential medication to treat CUD. However, Haney et al. [39] tested a range of cannabidiol doses (200–800 mg) in combination with active and placebo cannabis and found no cannabidiol effect on the subjective, reinforcing, or cardiovascular effects of smoked cannabis, providing little support for cannabidiol's utility as a medication to reduce cannabis' positive reinforcing and subjective effects.

Naltrexone

In light of the close anatomical and functional interaction between endogenous opioid and cannabinoid systems, naltrexone has also been investigated as a treatment for CUD. Although Cooper and Haney [18] reported that acute naltrexone pretreatment *increased* the positive subjective effects of cannabis in a human laboratory study [18], administration of naltrexone for several weeks *reduced* cannabis self-administration and its positive subjective effects in the laboratory and possibly also in the natural ecology [38]. Given these promising results, clinical treatment trials utilizing naltrexone maintenance therapy for CUD are supported.

Quetiapine

With the goal of reducing cannabis relapse by targeting specific withdrawal symptoms via non-cannabinoid medications, Cooper and colleagues [19] tested the effects of the atypical antipsychotic quetiapine on cannabis withdrawal and relapse. This medication antagonizes monoamine receptors to exert mood-stabilizing effects, appetite-stimulating effects, and hypnotic effects, suggesting it may suppress the full spectrum of cannabis withdrawal symptoms. Cooper et al. (2013) reported some positive effects of quetiapine in the human laboratory, including reversal of cannabis withdrawal-related anorexia, sleep disruption, and anxiety. However, quetiapine also intensified cannabis craving and increased cannabis self-administration after several days of cannabis abstinence. An open-label clinical trial of patients seeking treatment for CUD [67] showed that quetiapine was associated with decreased cannabis use, indicated by decreased self-reported spending on cannabis and decreased tetrahydrocannabinol-9-carbox-

ylic acid (THCOOH) urine levels. A randomized controlled clinical trial is currently underway to elucidate quetiapine's clinical utility for CUD.

Antidepressants

The first human laboratory studies examining medications for CUD tested antidepressants. Bupropion, an atypical antidepressant with inhibitory actions at primarily norepinephrine and dopamine reuptake transporters, reduces nicotine withdrawal and facilitates smoking cessation. However, in human laboratory studies of CUD, bupropion either worsened symptoms of cannabis withdrawal, including irritability, depression, and sleep disturbance [32], or had no effect [73] relative to placebo.

A similar drug, atomoxetine, has also been tested for treatment of CUD due to its inhibitory actions on noradrenergic and dopaminergic reuptake. Tirado and colleagues [83] tested this medication in an open-label trial of feasibility, safety, and tolerability but found no positive signal as a treatment for CUD. A later clinical trial confirmed these negative findings while also demonstrating the poor tolerability of the medication in cannabis users [69].

Haney et al. [33] also tested the antidepressant, nefazodone, in the human laboratory. In addition to mild-moderate antagonistic properties at alpha 1- and 2-noradrenergic receptors, nefazodone is a serotonin 2A receptor antagonist and a serotonin reuptake inhibitor. Nefazodone can alleviate agitation and anxiety [22] and has shown promise in reducing craving for cocaine [56]. One human laboratory study examined nefazodone for CUD [33] demonstrating that it reduced anxiety and muscle pain during cannabis withdrawal, but not disturbances in mood or sleep disturbances. A later clinical trial examining bupropion and nefazodone side by side also had negative findings, indicating that nefazodone has limited promise as a treatment for CUD, providing further evidence that medications that fail in the human laboratory are unlikely to succeed in the treatment clinic [14].

Mirtazapine, a tricyclic antidepressant, and potent antagonist of alpha 2A-, 2B-, and 2C-adrenergic receptors, as well as of 5-HT2A, 2C, and 3 receptors, has also been tested for CUD. Mirtazapine increases noradrenergic and serotonergic transmission [2] and has been shown, presumably through these mechanisms, to decrease agitation and insomnia in alcohol-dependent patients [64, 92]. Though mirtazapine robustly reversed anorexia and sleep disruption during cannabis abstinence in the human laboratory, there were no effects on mood or cannabis self-administration, consistent with other investigations of noradrenergic/serotonergic classes of medications [36].

Other classes of medications that have been studied using a human laboratory model include compounds acting at gamma-aminobutyric acid (GABA) sites, hypothesized to reduce the mood instability and agitation associated with cannabis withdrawal. The anticonvulsant divalproex was tested by Haney et al. [34]. The mechanisms of divalproex have not been fully elucidated, but it appears to exert its antiepileptic and mood-stabilizing effects via increasing GABA concentrations, suggesting it may reduce the negative mood symptoms experienced during cannabis withdrawal. Although, divalproex reduced cannabis craving, the medication was poorly tolerated, worsening both mood and cognitive task performance. These negative findings were replicated by a clinical trial examining divalproex for the treatment of CUD [60], which demonstrated no significant differences between divalproex and placebo with regard to treatment retention, cannabis craving, or abstinence. Thus, divalproex has shown little potential for the treatment of CUD. Haney et al. [36] also investigated the $GABA_B$ receptor agonist, baclofen, in an inpatient laboratory model of cannabis withdrawal and relapse. Although baclofen reduced cannabis craving in a dose-dependent manner, it had no effects on negative mood during withdrawal, did not reduce relapse, and worsened performance on cognitive tasks [36].

By contrast, some promising evidence of pharmacological treatment for CUD using human laboratory models is seen in studies of $GABA_A$ agonists. As mentioned earlier, the combination of zolpidem and nabilone was effective in reducing cannabis self-administration and cannabis withdrawal-related disturbances in mood and food intake, though this combination did result in slight increases in ratings of abuse liability. Further, zolpidem demonstrated efficacy for reducing sleep disturbances during withdrawal without increasing abuse liability [46]. Another laboratory study showed that zolpidem reduced sleep disturbances as measured by polysomnography, along with subjective ratings of sleep quality in daily cannabis users. Specifically, 3 days of cannabis abstinence reduced the total amount of sleep as well as sleep efficiency relative to phases of ad libitum cannabis use, which zolpidem attenuated [88]. Accordingly, this group is currently conducting a clinical trial to better understand the role of sleep disturbance in CUD and the potential of zolpidem to attenuate this symptom and thus improve quit rates.

Considerations of the Human Laboratory Model and Strategies for Moving Forward

Randomized, placebo-controlled clinical trials are the standard by which the efficacy of potential treatments is determined. Human laboratory studies are an essential precursor

to these large clinical trials, by (1) confirming that co-administration of the target medication and cannabis is safe and well-tolerated and (2) demonstrating whether the medication produces a positive signal, selectively reducing targeted behavioral endpoints such as cannabis self-administration and/or withdrawal symptoms during abstinence. Laboratory studies have the benefit of being able to carefully control for factors that may influence outcome, such as alcohol or other drug use, medication compliance, psychiatric comorbidities, and the influence of other extraneous variables. These models can also use within-subject repeated-measures designs, which provide ample statistical power to detect medication effects among small samples of well-screened research volunteers [28].

Further, laboratory studies can also monitor the effects of medications on outcomes not directly related to cannabis use but which influence medication tolerability, such as cognitive task performance and overall mood. As mentioned previously, divalproex (1500 mg/day) alone worsened mood and cognitive task performance in cannabis smokers, suggesting that these doses would be poorly tolerated in the outpatient treatment clinic [34].

But do human laboratory models predict medication efficacy clinically? Predictive validity is the most critical feature of models of treatment development. Studies of contingency management have yielded consistent findings in human laboratory studies and clinical trials, indicating efficacy of this nonpharmacological methodology to produce abstinence in non-treatment-seeking populations as well as those seeking treatment [9, 11, 15, 65, 79, 87]. Overall, the human laboratory studies that have investigated medications development for CUD have also had good correspondence with subsequent clinical trials, in terms of both positive and negative findings. For instance, the ability of dronabinol to significantly reduce symptoms of cannabis withdrawal was highly consistent across both laboratory [13, 34, 89] and clinical trials [62]. Human laboratory studies illustrating the inefficacy of bupropion, divalproex, and nefazodone for cannabis withdrawal [32–34] and the inability of dronabinol to reduce cannabis self-administration [35, 40] were also entirely consistent with clinical trial findings [14, 60, 62]. Although there are clearly more consistencies than inconsistencies, predictive validity cannot be determined until there are positive clinical trial data on a medication also tested in the human laboratory.

Though the aforementioned studies illustrated consistency in the transition from laboratory to clinic, there was a marked incongruence in the outcome of lofexidine and dronabinol in the laboratory relative to the clinic. Haney et al.'s [35] positive findings of combined dronabinol and lofexidine on cannabis withdrawal-induced sleep disturbances, craving, and relapse rates were not replicated in the clinic by Levin et al. [63], as the former was able to administer medication more frequently and at a higher daily dose, whereas in the latter outpatient setting, even lower daily doses were poorly tolerated. These findings highlight the importance of testing procedures in the human laboratory that would be feasible in an outpatient, clinical setting.

Outcomes: What Should the Goal Be?

Both human laboratory models and clinical trials of CUD focus on endpoints that include withdrawal symptoms, cannabis use, abstinence, and relapse rates. However, clinical trials testing treatments for alcohol use disorder typically recruit heavy drinkers and define a positive outcome as a reduction in the number of heavy drinking days [75]. Thus, it is possible that outcomes defining treatment efficacy as complete abstinence from cannabis may miss clinically meaningful reductions in use as a result of treatment. It is an empirical question, but it may prove more promising to seek reductions in cannabis use and improvement in quality of life measures when evaluating potential candidate medications for treatment of CUD. Measuring a reduction in cannabis use is admittedly difficult, as THC metabolites have a notably long elimination half-life, and detection rates have are highly variable between individuals following cannabis cessation, ranging from hours to over 1 month after last use [48]. Nonetheless, further work is needed to evaluate clinically meaningful outcomes other than total abstinence. For instance, there is a growing interest for the study of topography (i.e., puff strength, length, frequency, etc.) in cannabis research [68], a method which could prove useful as an ecologically valid measure of cannabis use.

To conclude, human laboratory models provide meaningful behavioral data in a relatively small number of individuals on the effects of the medication alone (e.g., its own potential for abuse, negative effects on mood, physical symptoms, cognition, sleep), as well as on how the medication alters the positive and negative reinforcing effects of cannabis. Overall, the studies reviewed here have dramatically increased our scientific understanding of the variables maintaining problematic cannabis use and are important in guiding the development of more effective treatments.

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Clinical Manifestations of Cannabis Use Disorder

10

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Introduction

Cannabis use disorder (CUD) or its colloquial synonym, cannabis addiction, remains controversial in that many in the general public believe that cannabis use does not pose substantial risk for harm and is not addictive in the same sense that tobacco, alcohol, cocaine, or heroin is addictive. Although assessment of people's beliefs about addiction and harm is complicated by the lack of a consensus definition or a common understanding of addiction, the difference in perception of risk between cannabis and other substances that are used recreationally is clear. For example, in the most recent Monitoring the Future (MTF) survey, when asked "how much do you think people risk harming themselves (physically or in other ways) if they smoke marijuana regularly?", only 32% of US 12th graders responded, "great risk," on a 5-point scale that ranged from no risk to great risk [1]. In comparison, responses of "great risk" were 85% for *take heroin regularly*, 81% for *take cocaine powder regularly*, 74% for *take any narcotic other than heroin regularly*, 76% for *smoke one or more packs of tobacco cigarettes per day*, 59% for *take 4–5 drinks (alcohol) nearly every day*, 54% for *take amphetamines regularly*, and 50% for *take sedatives regularly*. Note that the 32% response rate of "great risk" to regular marijuana use is down from 50% in 1980, 78% in 1990, 58% in 2000, and 47% in 2010. Indeed, it is lower than the previous lowest MTF survey rating by 12th graders, which was 35% in 1978. In contrast, the percentages of youth endorsing *great risk* for heroin have never ranged out of the mid to high 80s over this time period, and cocaine has ranged from its low of 68% in 1978 to a stable range of above 80% since 1986.

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That said, risk of "harm" differs conceptually from risk of "addiction." People may think that cannabis is addictive, but that cannabis addiction causes minimal harm. Alternatively, they may believe that the direct effects of a drug can hurt you physically (e.g., cause accidents or a stroke), but may not be addictive. A moderate-size study (n = 2002) of college-aged students conducted in 2013 suggests that cannabis is perceived as both less addictive and less harmful than other substances [2]. In response to the question, *How addictive do you think* (*drug name) is?,* students' average rating for marijuana was 4.1 (SD = 2.1) on a 7-point scale compared with 6.5 (SD = 1.0) for tobacco. In response to the question, *How harmful to your health do you think* (*drug name) is?*, their average rating was 4.6 (SD = 2.2) for marijuana compared with 6.4 (SD = 1.3) for tobacco. Other survey studies have reported similar findings [3, 4]. A 2014 Pew survey of the general US population asked which is more harmful to your health, alcohol or marijuana. The response favored alcohol (69%) over marijuana (15%) by a wide margin. Recently, we conducted an online survey that recruited 400 chronic pain patients who had used opiates and marijuana (unpublished data). Over 72% of respondents rated marijuana as *not addictive at all*, and another 18% rated it as only *slightly addictive*. Similarly, in another online survey of 2630 14–18-year-old cannabis users, 84% responded *no* to the question, *is cannabis addictive?* [5].

These types of observations suggest that current perceptions of the risk of becoming addicted or experiencing adverse consequences from cannabis use remain substantially lower than other commonly used psychoactive substances. Although such a comparative evaluation of cannabis may have some merit, the potentially exaggerated perception of low risk fosters significant concern, particularly because of the ongoing emergence of more potent and possibly more addictive cannabis products in the marketplace, simultaneous with this steadily decreasing trend in perceived risk for harm [6–8]. This chapter will address this issue in two ways. First, a cursory review of what is known scientifically about cannabis' addictive potential will clearly

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establish that cannabis use can develop into cannabis addiction. The second half of the chapter will focus on what is known about the clinical manifestations of CUD. That is, we will describe the features of cannabis addiction that are most concerning and the harms that are experienced by those who develop a CUD.

Part I. How Do We Know Cannabis Has Addictive Potential? How Addictive Is It?

Definition of CUD Before one can discuss whether or not a substance is addictive, an agreed upon definition of addiction is needed. Here, we will primarily rely on the *Diagnostic and Statistical Manual of Mental Disorders* definition and criteria to frame this discourse [9, 10]. The DSM-5 generic criteria for all substance use disorders (SUDs) are presented in abbreviated form in Table 10.1. The DSM states, "The essential feature of a substance use disorder is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems." A pathological pattern of behavior related to substance use is demonstrated by meeting criteria across multiple related dimensions: impaired control, social impairment, risky use, and pharmacological/physical signs of excessive substance use. Arguably, the inclusion of CUD in the DSM, and in its international parallel, the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) [11] indicates that the medical and scientific communities consider CUD a reliable and valid diagnostic category of mental disorder that individuals in the general population experience in much the same way as they experience other SUDs. Such status within these diagnostic systems indicates that CUD is a clinically important disorder with substantial scientific data characterizing its phenomenology, prevalence, course, and functional consequences.

Table 10.1 DSM-5 substance use disorder criteria

Impaired control
1. Longer/larger: using in larger amounts or for longer periods than intended
2. Quit/control: persistent desire to or unsuccessful efforts to reduce use or quit
3. Time spent: great deal of time spent obtaining, using, and recovering
4. Craving: strong desire or urge to use
Social impairment
5. Neglect roles/obligations: failure to fulfill obligations at home, work, or school
6. Continued use: use despite having interpersonal/social problems related to use
7. Reduced/discontinued activities: less time spent in important social, occupational, or educational activities
Risky use
8. Use in hazardous situations: recurrent use in situations that could result in harm
9. Medical/psychological problems: continued use despite awareness of that it is causing or worsening such problems
Physiological/pharmacological
10. Tolerance: need for increased amounts to achieve desired effects or diminished effects with same amount of use
11. Withdrawal: experience the characteristic syndrome when discontinuing use, or using to avoid or relieve the symptoms of the syndrome

Empirical Evidence for CUD

Nonhuman and human laboratory, genetic, epidemiological, and clinical studies converge to demonstrate the biological plausibility, the existence, prevalence, and clinical importance of CUDs [12]. Here, we briefly touch on this body of evidence.

Biological Plausibility

Preclinical and clinical research has clearly demonstrated how cannabis exerts its effects on humans and has identified and characterized the human endogenous cannabinoid system. The psychoactive and reinforcing effects of cannabis are primarily mediated by activation of cannabinoid receptors in the brain [13]. Two receptor subtypes (CB1 and CB2) have been identified. Activation of the CB1 receptor by the delta-9 tetrahydrocannabinol (i.e., THC) compound found in the cannabis plant triggers the positive reinforcing effects of cannabis use (i.e., perceived pleasurable feeling or sensation). THC's effect on the CB1 receptor enhances neuronal dopamine firing and synaptic dopamine levels in the reward pathway of the brain [14], which is a neurobiological feature of most all psychoactive substances with substantial abuse potential. Likewise, a multitude of studies has clearly linked this neurobiological system to the phenomenon of cannabis withdrawal, a hallmark symptom of most SUDs (cf. [15, 16] see Chap. 12 (Cannabis Intoxication) in this book). Such research has demonstrated how THC deprivation can precipitate withdrawal, how CB1 agonists (e.g., THC) can relieve withdrawal that follows discontinuation of THC administration, and that CB1 antagonists can precipitate withdrawal in animals that have been administered CB1 agonists. In summary, the neural processes observed related to cannabis administration and withdrawal parallel those of most substances that carry risk for development of an addiction.

Genetic influences also contribute to the development of CUD, similar to that observed with other SUDs. Heritable risk factors contribute to between 30% and 80% of the total variance in risk of developing a CUD, and genetic linkage studies strongly suggest a genetic link to CUD [17].

Substance-specific genes have been identified that impact vulnerability to the addictive potential of cannabis. Other genes that increase or decrease genetic vulnerability to externalizing behavior problems in general, including adolescent experimentation and misuse of psychoactive substances, have also been linked to cannabis use and misuse. Last, certain genes that impact reactivity to environmental variables such as stress, and thus influence risk for substance misuse, have been associated with CUD.

Prevalence and Probability of CUD

The prevalence of CUD in the general population of the USA and elsewhere is typically only exceeded by substances that are legal and available for purchase, i.e., alcohol and tobacco. Data from the National Comorbidity Survey in the early 1990s indicated that lifetime prevalence of any cannabis use in the USA was 46%, and approximately 9% of those who had ever used cannabis in their lifetime had developed a CUD [18]. More recently, analyses from the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC) indicated that the prevalence of lifetime and past-year CUD diagnoses in the adult (18+) US population were approximately 6.3% and 3%, respectively [19]. The past-year prevalence of CUD, among adults who reported using cannabis during the past year, was approximately 30%. Of note, substantially more conservative estimates were observed in the 2013 National Survey on Drug Use and Health (NSDUH). These data indicated a past-year CUD prevalence of 1.5% in the general US adult population and 11.6% among past-year cannabis users compared to the estimates of 3% and 30% from the NESARC data [19, 20].To provide context for these prevalence data in relation to other substances, consider the following NESARC data. Past-year prevalence of alcohol use disorder was 13%, and approximately 17.5% of past-year alcohol users met criteria for alcohol use disorder [21]. For tobacco, prevalence of past-year tobacco use disorder was 20%, and the prevalence of a use disorder among those using in the past year was approximately 80% [22]. Based on these NESARC findings, the probability that a current cannabis user has developed a CUD is greater than alcohol users having an alcohol use disorder but much lower than current tobacco users having a tobacco use disorder. Comparison with an illicit substance, cocaine, gleaned from the 2015 NSDUH, showed that 1.8% of the US population had used cocaine in the past year, and 18% of these past-year users had a cocaine use disorder [23]

Of further note, among past-year cannabis users, ethnic minorities (e.g., African Americans, Hispanics, and Native Americans) have a higher likelihood of being weekly cannabis users and having a CUD than Caucasians. Additionally, younger adults [18–25], males, those with lower education and incomes, and those with other psychiatric disorders are at increased risk for having a current CUD [24–26].

Part II. Clinical Manifestations of CUD

CUD Severity Our prior reviews of the CUD literature concluded that the diagnostic features of CUD closely parallel most other SUDs [27, 28]. A wide range of studies converged on the conclusion that the generic DSM SUD criteria, when applied to CUD, are stable and reliable, reflect a unidimensional construct, utilize the full range of criteria, and perform as well for cannabis as for other substances [27]. That said, across studies, the expression of CUD tended to be less severe, on average, than most other SUDs in terms of the mean absolute number of use disorder criteria observed per diagnosis. Moreover, we have noted that cannabis withdrawal, which was only first included as a CUD criterion in the most recent version of the DSM, is clinically important in maintaining problematic use and in precipitating relapse; however, such withdrawal is not associated with major medical or psychiatric risks or consequences [15] (also see Chap. 11 (Cannabis Withdrawal) in this book).

More recent, rigorous studies on the reliability and validity of the diagnosis of CUD compared with other SUDs support the conclusions from our early reviews [29, 30]. A comprehensive review over 30 epidemiological and clinical studies concluded that the generic DSM SUD criteria set appears equally applicable across substances, with no substantial exceptions related to CUD [30].

Severity data from the most recent wave of NESARC found that slightly more than half of current adult CUD cases could be classified as mild (2–3 criteria) with the remainder evenly split between moderate (4–5 criteria) and severe (6 or more criteria) (see Table 10.1 for CUD criteria) [31]. These survey data also revealed a number of clinically important observations. The more severe the CUD, the more likely one is to have a comorbid psychiatric disorder including posttraumatic stress disorder, depression, panic disorder, social phobia, borderline personality disorder, and other SUDs. CUD severity was also positively related to level of disability as assessed by the Short Form Health Survey, with the largest impairment observed on role-emotional functioning domain of this measure, reflecting difficulty in accomplishing daily/work tasks due to emotional problems. Last, increased CUD severity was related to increased use of clinical services for problems related to cannabis use.

Clinical Features/Phenomenology of CUD Adults participating in clinical trials for the treatment of CUD and daily cannabis users in natural history studies typically report cannabis use for many years with the great majority initiating

cannabis during their teenage years [32–37]. Most of these individuals have been using cannabis multiple times per day on an almost-daily basis and are thus under the influence or intoxicated for much of a typical day. The majority of those seeking treatment for CUD, including adolescents, report a history of cannabis withdrawal symptoms [38–40]. The most frequently reported problems related to their cannabis use among treatment-seeking adults are procrastination/low productivity, memory issues, low energy, financial or employment difficulties, guilt about use, cannabis withdrawal, low self-confidence/self-esteem, insomnia, and distressed personal relationships [32, 41, 42]. In addition, many of those with CUD frequently report continued cannabis use despite recognizing its negative effects on medical (e.g., chronic cough or bronchitis) or psychological problems (e.g., exacerbation of mental health disorders). Other observations reported for adults with CUD include high use of health-care services, reports of low quality of life, and underemployment [43–46].

For youth in treatment for CUD, first use of cannabis is typically before 15 years of age. Frequency of use is more variable than that observed in adults. More youth report non-daily use and more report episodic use patterns and binges [47–49]. Cumulative data from a number of clinical trials for youth indicate that the most frequent problems endorsed on the Marijuana Adolescent Problems Inventory were went to work or school high (79%), neglected responsibilities (56%), not able to do homework or study (54%), tried to cut down or quit (54%), tried to control their use (52%), felt they needed more cannabis to get the same effect (48%), missed school or work (40%), told by a friend to cut down use (39%), missed out on things because they spent too much money on cannabis (38%), had a bad time (37%), had a fight or argument with family (35%), continued use despite promising oneself not to (35%), and noticed an unpleasant change in personality (33%) [50]. Interestingly, despite these rates of endorsement, only 34% of these teens indicated that they had a problem with cannabis. In addition, youth with more severe CUD are more likely to report engaging in risky sexual behavior and to experience more physical health problems and comorbid mental health issues [47]. In summary, although those entering treatment for CUD may not generally experience as severe of consequences or crises as those entering treatment with alcohol, cocaine, or opioid use disorders, they clearly show impairment that warrants clinical attention.

Co-occurring SUDs and Mental Health Problems Comorbidity of CUD and other mental disorders including SUDs is commonly observed in both clinical and general population samples (see Chap. 15 for a comprehensive overview of psychiatric comorbidities). For example, the 2015 report from the Treatment Episode Data Set (TEDS), a yearly report from SUD treatment programs who receive federal funding, indicated that 35% of individuals 12 years and older who endorsed cannabis as the primary problematic substance also evidenced at least one additional psychiatric disorder, including other SUDs [51]. Most clinical trials for CUD unfortunately exclude participants with other psychiatric conditions and thus do not provide highly useful information on co-occurring disorder diagnoses.

Large general population clinical epidemiological surveys like the NESARC indicate that CUD co-occurs with other psychiatric conditions at a high rate [31]. Having a CUD in the past 12 months substantially increases rates of (a) most psychiatric conditions [any mood disorder (OR = 3.8), major depressive disorder (OR = 2.8), any anxiety disorder (OR = 2.8), posttraumatic stress disorder (OR = 4.3), and any personality disorder (OR = 4.8)] and (b) other SUDs [any SUD (OR = 9.3), alcohol use disorder (OR = 6.0), any drug use disorder (OR = 9.0), and nicotine use disorder (OR = 6.2)]. Moreover, the probability of having other psychiatric disorders and SUDs increases with greater severity of the CUD [31].

Disorders that co-occur with CUD are not necessarily clinical manifestations of CUD; that is, the aforementioned data do not indicate that cannabis use or CUD causes the occurrence of these other problems. Whether mental health or substance use problems contribute to development of CUD, or the converse, remains equivocal. A recent report from a clinical trial of medication and behavioral therapy for CUD observed a longitudinal relationship between reductions in cannabis use during the 12-week treatment and improvements in anxiety, depression, and sleep quality [52]. Detailed discussion of implications of such findings and this complex issue in general are beyond the scope of this chapter. Of importance here is the recognition that these co-occurring problems are commonly observed with CUD, vary by CUD severity, and contribute to the difficulty in assessing and treating those with CUD.

Cannabis Cessation, Treatment Involvement, and Outcomes Data from natural history studies and clinical trials illustrate how difficult it is to quit cannabis use once an individual has developed CUD or established a regular pattern of daily use. A prospective study of daily cannabis users who were "probably or definitely planning to reduce or quit in the next 3 months" showed that over 3 months, these users made many bidirectional transitions among usual use, reduction in use, and abstinence. Quit and reduction attempts were short-lived with very few participants achieving longer-term abstinence [36, 37].

Cannabis users with CUD commonly end up receiving treatment for their CUD. The TEDS data indicate that in 2015 treatment cases for which cannabis was reported as the primary substance of misuse represented 14% of all substance use treatment admissions (12 years and older) [51]. The

percentage of admissions of cases for CUD decreases by age. For example, for youth 12–17 years old, cannabis was the primary substance in approximately 77% of cases; for those aged 18–19, it was 44%; for 20–24 years, it was 22.5%; and for 25–34 years old, it was approximately 12% of cases. A study of adolescents' electronic medical records in a general community sample confirmed that CUD is disproportionally represented as the primary problematic substance across treatment settings, i.e., more than 80% of all youth SUD cases [53]. Of additional importance is that in addition to CUD being a highly prevalent primary problem, it is also the most common secondary or tertiary substance of abuse (20% of all admissions) reported among individuals 12 years and older [51]. Approximately 89% of adolescent treatment admissions involved cannabis as a primary, secondary, or tertiary substance.

Adults who enroll in CUD treatment perceive quitting to be difficult and many report having made multiple unsuccessful attempts to quit [32, 35, 54]. To date, medications tested in pharmacotherapy trials for CUD have generally not been effective for engendering cannabis abstinence or significant reductions in use. In the few studies that have observed positive findings, the medications had little therapeutic effect on the great majority of participants [55–57]. Outcomes observed with psychosocial treatments (motivational enhancement, cognitive-behavioral, and contingency management interventions) for CUD have been more positive, particularly for adults [28, 56, 58, 59]. Positive 6-month outcomes (i.e., abstinence or substantial reduction in use) have ranged from 20% to 45% with well-specified behavioral treatments. Such efficacy data for CUD interventions for adults indicate that it is not easily treated, with rates of successful outcomes relatively comparable to treatments for other substances [28, 56, 58, 59].

Treatment outcomes for adolescents receiving treatment for CUD also show much room for improvement. The only positive pharmacotherapy trial for youth CUD showed that N-acetylcysteine (NAC) had a modest during-treatment effect on cannabis abstinence [60]. Thirty-six percent of youth who received NAC plus abstinence-contingent reinforcement were abstinent from cannabis during the last 2 weeks of an 8-week intervention vs. 22% of those who received placebo plus abstinence-contingent reinforcement. Confirmed cannabis abstinence at a 4-week, follow-up assessment was 19% vs. 10% for NAC vs. placebo, respectively.

Psychosocial treatments for youth CUD have received much more attention than medication studies. Family-based, individual, and group outpatient therapies have demonstrated efficacy for adolescent SUDs, with cannabis being the primary substance used [61–64]. Although helpful to many youth, the majority that receive these interventions typically do not show a clinically meaningful reduction in substance use, and posttreatment assessments indicate substantial relapse among those who do respond. For example, the largest trial of psychosocial treatments assigned youth to one of five well-specified, empirically based treatments [65]. Significant decreases in cannabis use and CUD symptoms were associated with all treatments, yet, no robust between-treatment differences were observed. Reductions in use across treatments were promising compared with those observed in prior studies. Nonetheless, an estimated two-thirds of these adolescents continued to experience significant substance-related symptoms at the end of the 3-month treatment period. Most never achieved substantial reductions in cannabis use or abstinence, and many of those who are initially successful relapse. In summary, the modest positive outcomes observed following treatment for adult and youth CUD indicate a pressing need for development of more intervention models that can substantially impact the clinical manifestations of CUD, both short- and long-term.

Cognitive and Behavioral Functioning Laboratory studies demonstrate that cannabis use can adversely impact behavioral and cognitive functioning [66–70]. The implications of these findings suggest that cannabis use can interfere with optimal performance at work or school, increase risk of harm or accidents when engaging in activities that could be physically hazardous, and increase the probability of engaging in risky behavior due to poor judgment (e.g., driving a car, playing certain sports, operating machinery or engaging in other work activities, engaging in unprotected sex). This body of research has focused on the impact of *cannabis use* and not necessarily CUD. However, the cannabis use patterns characteristic of those with CUD (e.g., early age of onset and frequent and regular use) typically comprise the use characteristics associated with cognitive and behavioral performance deficits. Indeed, many of the problems reported by adults and adolescents with CUD can result from or be exacerbated by the direct pharmacological effects of intoxication and chronic use. Of great concern is the magnitude of these effects on youth whose brains and neurodevelopment processes are yet to fully develop [71]. Whether or not or how long it may take one to regain optimal functioning following discontinuation of cannabis use also remains uncertain [70]. Clearly, however, many of those with CUD, youth and adults alike, evidence mild to moderate impairment in functioning related to cannabis use that is likely to adversely impact their capacity for optimal performance across multiple domains.

Conclusion and Summary Points

Cannabis use disorder is real, is relatively common, manifests in consequences similar to other SUDs, and is not easily treated. The scientific and clinical literature on cannabis, i.e., the neurobiological and behavioral processes involved in its effects and functional consequences, provides unequivocal

evidence for the existence and clinical importance of CUD. Of imminent concern, the public health problems associated with CUD may increase further with the proliferation of legal cannabis laws, particularly if attention is not paid to the factors that influence the development and maintenance of CUD, e.g., access, potency, route of administration, and marketing [72]. Current perceived risk of harm from regular cannabis use is at an all-time low, which escalates such apprehensions, particularly for adolescents and young adults. These younger age groups are clearly most vulnerable to both the risk of developing a CUD and the consequences of regular cannabis use on their developing brain structure and function. Currently, most adolescents and adults do not appear to believe that cannabis use has the potential to develop into an addiction, and even if they do, they think the implications of CUD are not cause for substantial concern. The development of effective strategies for how to change such beliefs and perceptions warrants consideration as a public health priority. Like all other psychoactive substances that are misused and for which an addiction can develop, most individuals who initiate cannabis use do not experience significant consequences; however, a significant subset go on to develop a CUD that ranges from mild to severe, and these people experience significant functional consequences.

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Cannabis Withdrawal

11

Nicolas J. Schlienz and Ryan Vandrey

Introduction

Drug withdrawal refers to a constellation of symptoms that occur following abrupt cessation of chronic drug use. Though drug withdrawal can occur from stopping use of medication, it is most often encountered within the context of illicit, non-medicinal, drug use. The withdrawal symptoms that emerge following extended and frequent use of abused drugs are a key feature of what define substance use disorders [4, 85]. Further, there is accumulating neurobiological evidence that withdrawal drives the maintenance of problematic substance misuse through a mechanism of reward dysfunction and negative reinforcement [52]. Historically, there was debate and controversy regarding the existence of a valid and clinically meaningful cannabis withdrawal syndrome. However, extensive translational research has now firmly established that cannabis withdrawal occurs reliably in a subset of cannabis users, that it is pharmacologically specific to the use of cannabis, and that it is clinically meaningful within the context of treating cannabis use disorder (CUD). As a result, mitigating cannabis withdrawal has been targeted in several studies aiming to develop improved treatments for CUD (discussed in detail in other chapters of this book). There are also individual characteristics, such as sex, genetics, and co-occurring psychiatric disorders that have been associated with differences in the type or severity of cannabis withdrawal. This chapter will provide a detailed overview of the etiology and characterization of cannabis withdrawal with emphasis on its importance within the context of CUD.

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Phenomenology

Following an extended period of daily heavy use, termination of cannabis use is associated with the onset of a cannabis withdrawal syndrome that has been well-documented; has been observed in humans, rodents, and nonhuman primates; and has been reported in inpatient, outpatient, and clinical research settings [12, 14, 42].

Symptoms and Time Course

Symptoms Early controlled laboratory studies of cannabis withdrawal reported the onset of a series of withdrawal symptoms that emerged after a period of unrestricted cannabis self-administration. Following cessation from cannabis use in a controlled residential research unit, an inpatient sample of heavy users reported increased ratings of "anxiety," "irritability," and "stomach pain" [45]. Findings from multiple outpatient studies documented symptoms that also included anger, aggression, physical tension, nervousness, restlessness, depression, sleep difficulties, and loss of appetite [16, 55, 56]. The set of cannabis withdrawal symptoms that are most common, elicited reliably, and constitute DSM-5 cannabis withdrawal syndrome symptomatology [4] are outlined in Table 11.1 and include the following: irritability, anger/aggression, anxiety, sleep disturbance, appetite decline or weight loss, restlessness, and depressed mood. Less common symptoms include shakiness, chills, sweating, nausea/stomach pain, and tension [15, 43, 45, 55].

Time Course Findings from early investigations of cannabis withdrawal provided an initial understanding of symptom characteristics and demonstrated that symptoms generally emerge within 24–72 h following cessation from cannabis [15] and reach peak magnitude 2–5 days post-cessation [15, 44, 45, 55]. Studies conducted by Budney and colleagues [15] and Kouri and Pope [55] provided a broader understanding of the time course of cannabis withdrawal

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Table 11.1 DSM-5 cannabis withdrawal diagnostic criteria

Criterion A	Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months)
Criterion B	Three (or more) of the following signs and symptoms develop within approximately 1 week after Criterion A: 1. Irritability, anger, or aggression 2. Nervousness or anxiety 3. Sleep difficulty (e.g., insomnia, disturbing dreams) 4. Decreased appetite or weight loss 5. Restlessness 6. Depressed mood 7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
Criterion C	The signs and symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
Criterion D	The signs or symptoms are not attributable to another condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance

based on self-reported symptoms during an extended period of abstinence. Most withdrawal symptoms resolve within 2–3 weeks and return to baseline levels [15, 55]. However, abstinence-induced insomnia may continue to persist, and reports of abstinence-related increases in vivid or strange dreams failed to return to baseline levels at the end of a 45-day abstinence period [15].

Validity, Reliability, and Clinical Significance

For years, the proposed existence of a cannabis withdrawal syndrome was met with great skepticism, and one early review of the literature concluded that the combination of methodological limitations of published findings and lack of controlled research rendered the recognition of a cannabis withdrawal syndrome as being premature [75]. However, an extensive body of research has now clearly demonstrated that the cannabis withdrawal syndrome is valid, reliable, and pharmacologically specific and produces distress and impairment in important areas of functioning [12, 14, 42].

Reliability Core symptoms of cannabis withdrawal have been consistently documented in adults [13, 16, 43, 45, 55], adolescents [25, 26, 30, 32, 41, 68, 69, 77], and individuals with polysubstance use and comorbid psychopathology [9, 19, 49, 54, 82], and within incarcerated samples [70, 71, 76]. Further, cannabis withdrawal symptoms have been documented in treatment-seeking and non-treatment-seeking populations and across inpatient and outpatient settings. Thus, cannabis withdrawal is consistently observed across a variety of daily cannabis users and differs from data obtained from control samples of individuals who do not use cannabis [15, 55].

Pharmacological Specificity In addition to establishing the reliability of cannabis withdrawal, it must be demonstrated to be pharmacologically specific in order to be considered a valid withdrawal syndrome [12]. Preclinical and human laboratory studies provide clear evidence that cannabis withdrawal is mediated by the impact of chronic cannabis use on the CB1 receptor. Specifically, studies in nonhuman species show that withdrawal can be elicited via spontaneous cessation or administration of the CB1 inverse agonist SR141716A in animals chronically administered a CB1 agonist (e.g., THC, WIN55,212-2, CP55,940; for review see [60]). In contrast, withdrawal was not elicited by SR141716A in CB1 knockout mice chronically treated with THC [57]. In the human laboratory, multiple studies have demonstrated that cannabis withdrawal abates with either a return to cannabis use or the administration of oral THC [13, 17, 43, 81], but not with the administration of cannabis in which THC has been removed. A neuroimaging study showed that daily cannabis users had fewer CB1 receptors compared with matched controls and that the downregulation of CB1 receptors resolved within 30 days of supervised abstinence [50]. Though the change in regionally specific CB1 receptors was not significantly correlated with cannabis withdrawal in that study (possibly due to a relatively small and homogeneous sample), the degree of CB1 downregulation was positively correlated with years of cannabis use, and the time course of CB1 receptor rebound during abstinence is consistent with the time course of cannabis withdrawal. In summary, converging evidence indicates that cannabis withdrawal is pharmacologically specific to the administration of THC (via CB1 agonism) and likely results from neurobiological changes in the CB1 receptor that occur with long-term, frequent cannabis use.

Clinical Significance As discussed in the *Diagnostic and Statistical Manual for Mental Disorders (DSM)*, a valid drug withdrawal syndrome must produce clinically significant impairment or distress (Table 11.1). Evidence of this comes from several research studies. First, two outpatient studies demonstrated that withdrawal-related distress is

apparent to independent observers when daily cannabis users abruptly quit [13, 15]. In these studies, friends and family members of study participants reported observing increased aggression, anger, irritability, restlessness, and nervousness during periods when participants were not using cannabis compared with when they used cannabis. Spontaneous reports from observers to study staff in some cases indicated that cannabis abstinence resulted in changes in behavior or mood severe enough to negatively impact interpersonal relationships and raised concerns about the ability of the cannabis user to appropriately care for his/her children [15]. In other studies, the majority of non-treatment-seeking adult cannabis users indicated that cannabis withdrawal directly contributed to the decision to resume cannabis use during a quit attempt or was the motivating factor for use of other substances including alcohol, tobacco, and sedatives [18, 23, 59]. Recent work has also examined the relationship between cannabis withdrawal severity and functional impairment. In a controlled laboratory study of non-treatment-seeking heavy cannabis users that agreed to abstain from cannabis use for 2 weeks, prospective assessments of total cannabis withdrawal severity accounted for 51% of the variance in a hierarchical model examining predictors of functional impairment attributed to cannabis withdrawal [2]. Thus, the clinical significance of cannabis withdrawal is established by data consistently indicating that withdrawal is noticeable to observers, interferes with psychosocial functioning, directly contributes to failed quit attempts, and increases other substance use among those trying to quit.

Similarity to Other Withdrawal Syndromes

Across drugs of abuse, the expression and central characteristics of drug withdrawal syndromes include a constellation of symptoms that include behavioral, affective, and physical symptoms (for details see [84]) and, importantly, hold important treatment implications. Adapted from Vandrey et al. [79], Table 11.2 lists the symptoms of cannabis withdrawal that are also consistently observed in other drug withdrawal syndromes. Sleep disturbance, restlessness, change in appetite/weight, and mood disturbances are consistently observed symptoms of withdrawal across drugs of abuse. Overall, symptoms of the cannabis withdrawal syndrome share the most overlap with tobacco withdrawal, a finding that has been documented in both between- and within-subjects studies [18, 78, 79]. The key difference between cannabis withdrawal and nicotine withdrawal is that there are opposing effects on appetite and change in body weight (appetite and weight decrease during cannabis withdrawal and increase during tobacco withdrawal). Similarities and differences in the time course of cannabis and other withdrawal syndromes are summarized in Table 11.3. Symptoms of cannabis withdrawal

Table 11.2 Cannabis withdrawal symptoms present in other DSM-5 withdrawal syndromes

	Cannabis	Tobacco	Alcohol	Stimulants	Opioids
Abdominal pain[a]	X	–	–	–	–
Anger/aggression	X	X	–	–	–
Anxiety/nervousness	X	X	X	–	X
Appetite change	X	X	–	X	–
Autonomic hyperactivity	–	–	X	–	–
Depressed mood	X	X	–	X	X
Diarrhea	–	–	–	–	X
Difficulty concentrating	–	X	–	–	–
Fatigue	–	–	–	X	–
Fever/chills/sweating[a]	X	–	X	–	X
Hallucinations	–	–	X	–	–
Hand tremor	–	–	X	–	–
Headache	X	–	–	–	–
Irritability	X	X	–	–	X
Lacrimation/rhinorrhea	–	–	–	–	X
Muscle aches	–	–	–	–	X
Nausea/vomiting[a]	–	–	X	–	X
Psychomotor agitation/retardation	–	–	X	X	–
Restlessness	X	X	X	X	X
Seizures	–	–	X	–	–
Sleep difficulty	X	X	X	X	X
Strange dreams	X	–	–	X	–
Weight change	X	X	–	X	–

Note: "X" denotes the presence of a symptom
[a]Less common cannabis withdrawal symptoms

Table 11.3 Comparison of time course of cannabis withdrawal with other drug withdrawal syndromes

	Cannabis	Tobacco	Alcohol	Stimulants	Opioids
Onset	24–48 h	2–12 h	4–12 h	24 h	6–12 h
Peak	2–5 days	2–3 days	2–3 days	2–3 days	1–3 days
Duration	2–3 weeks	3–4 weeks	1–2 weeks	2–3 weeks	2 weeks

tend to emerge much more gradually (i.e., 24–48 h) compared with tobacco, alcohol, or opioid withdrawal. However, the time to peak withdrawal effects (2–5 days) and the overall duration of withdrawal (2–3 weeks) for cannabis are comparable to that which is observed for other substances [51].

Neurobiological Mechanisms

Identification of Δ^9-tetrahydrocannabinol (THC), the primary psychoactive constituent of the cannabis plant [67], and discovery of the elements that comprise the endocannabinoid system have provided a framework for understanding the neurobiological underpinnings of the cannabis withdrawal syndrome.

Cannabinoid Receptors

Discussed previously, preclinical data provide overwhelming support for the mediating role of the CB1 receptor in cannabinoid reinforcement, tolerance, and withdrawal [61]. In rodents, the role of the CB1 receptor in the expression of cannabinoid withdrawal has been predominantly examined using precipitated withdrawal paradigms [60]. Following repeated treatment with CB1 agonists (e.g., THC, CP 55,940, WIN 55,212-2), administration of the CB1 antagonist SR141716A precipitates cannabinoid withdrawal that is manifested by behavioral and somatic symptoms such as wet-dog shakes and forepaw tremors [60]. Related administration of CB1 agonists in preclinical studies is associated with a reduction in CB1 receptor availability (i.e., receptor downregulation) that reflects the development of cannabinoid tolerance [61].

Recently, demonstration of CB1 receptor downregulation was also demonstrated in a human laboratory study. Daily cannabis users completed positron emission tomography (PET) imaging before and after a 30-day residential cannabis detoxification [50]. Compared with healthy controls, the daily cannabis users exhibited reduced (approximately 20% less) CB1 receptor density in the neocortex and limbic cortex, but not in the basal ganglia, midbrain, thalamus, pons, or cerebellum during the first PET scan (before detoxification). Following the 30-day abstinence period, however, the CB1 receptor downregulation in the neocortex and limbic cortex had reversed and was no longer different from healthy controls. Notably, CB1 receptor downregulation in this study was more pronounced among individuals with a longer history of cannabis use.

The demonstration of CB1 receptor downregulation in daily cannabis users was subsequently replicated [28]. Interestingly, CB1 receptor downregulation among daily cannabis users compared with healthy controls was observed across brain areas in this study and was found to be reversed after only 2 days of supervised cannabis abstinence. Further, the density of CB1 receptors was found to be inversely associated with cannabis withdrawal in that study.

Endocannabinoid Enzymatic Degradation and Inhibition

Whether variability in levels of endogenous cannabinoids influences cannabis withdrawal has been evaluated in preclinical and human laboratory research. Briefly, the primary endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), low- and high-efficacy agonists at the CB1 receptor site, respectively [33, 62]. AEA and 2-AG are produced on demand and degraded by the catabolic enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. Thus far, the results of precipitated withdrawal paradigms in FAAH knockout mice have yielded equivocal findings. In one study, administration of FAAH and MAGL inhibitors reduced signs of precipitated withdrawal in mice treated with THC, but the impact of inhibiting the degradation of AEA and 2-AG was comparable between FAAH (−/−) and FAAH (+/+) mice [73]. In contrast, AEA attenuated rimonabant-precipitated withdrawal in FAAH (−/−) mice [36]. At the time of this writing, there are currently no published findings from studies investigating the impact of FAAH inhibition on cannabis withdrawal in humans. However, preliminary findings from one clinical trial (ClinicalTrials.gov Identifier: NCT01618656) demonstrated that administration of FAAH inhibitor PF-04457845 reduced withdrawal and cannabis use behavior compared to placebo [27]. Though research evaluating the therapeutic potential of pharmacological agents that target endogenous cannabinoid levels has not been fully examined, developments in this topic area are encouraging, and it remains to be determined whether preclinical findings are able to be translated to the human laboratory.

Individual Differences

Similar to other drug withdrawal syndromes [84], self-report ratings of cannabis withdrawal are subject to interindividual variability and may be influenced by factors such as socioeconomic and demographic variables, cannabis use characteristics, and interactions with co-occurring psychiatric conditions and polysubstance use.

Demographics

Relatively few studies of cannabis withdrawal have been conducted to evaluate differences in withdrawal expression by demographic characteristics. This may be due to the fact that most controlled studies of cannabis withdrawal have been conducted with relatively small and mostly homogeneous samples. In one study of non-treatment-seeking cannabis users, older adults were more likely to report increased anxiety and less likely to report increased sex drive during a previous period of sustained cannabis abstinence compared with younger adults [24]. Across two studies of cannabis treatment seekers, retrospective ratings of withdrawal during the last period of sustained abstinence among adults [16] and adolescents [77] showed that similar symptoms were endorsed in both samples, but the adults had a higher rate of withdrawal symptom incidence and severity compared with the younger cohort. However, age-related differences in the type or severity of cannabis withdrawal symptoms were not found in several other studies limited to adults [3, 59, 69]. Two studies evaluated the impact of race on cannabis withdrawal. In a study of non-treatment seekers, African American cannabis users were less likely to report anxiety, craving, sleep difficulty, and depression compared to Caucasians but were more likely to report increased libido [24]. However, in a second study of non-treatment seekers, African Americans were qualitatively more likely to report cannabis withdrawal, but this effect was not statistically significant [59]. Interestingly, one recent report indicated that there may be a genetic component to the development of cannabis use disorder, including the presence and severity of withdrawal [34].

A number of preclinical and human studies have evaluated sex differences in cannabis withdrawal. In one study of Sprague-Dawley rats treated with THC, significant reductions in locomotor activity were more common among females compared to males following abrupt THC withdrawal, and, in another, females spent significantly less time in the open arm of an elevated plus maze (preclinical model of anxiety) compared to males ([46]; c.f. [64]). In a survey of non-treatment-seeking adult cannabis users, females endorsed a significantly greater number of withdrawal symptoms during a prior quit attempt and were more likely to experience withdrawal overall. In a similar study, females were less likely to report craving and increased sex drive compared to males but were more likely to report upset stomach during previous quit attempts [24]. In a sample of treatment-seeking adults, females reported more severe total withdrawal and a greater number of individual withdrawal symptoms compared to males [48]. As described previously, preclinical data provide compelling evidence of a sexually dimorphic endocannabinoid system [5, 29, 37], and this may account for the significant differences between males and females in the presentation of cannabis withdrawal.

Cannabis Use History and Characteristics

The impact of prior cannabis use characteristics on withdrawal symptom expression during abstinence has been examined in a subset of cannabis withdrawal studies. Among non-treatment-seeking adults, greater lifetime cannabis use was found to increase the likelihood of experiencing withdrawal, and, additionally, the endorsement of at least weekly use was associated with significantly greater cannabis withdrawal severity compared with less frequent use [59]. Similarly, among frequent cannabis users, the total amount of cannabis consumed in the month preceding the quit attempt was positively associated with the total number of withdrawal symptoms reported, though the strength of this association was small [38]. In contrast to this, other studies of treatment-seeking adolescents and non-treatment-seeking adults failed to observe a significant relationship between quantity of cannabis use and withdrawal severity [3, 68].

Comorbid Psychopathology

Findings from laboratory studies and recent population survey estimates indicate that individuals with substance use disorders also report co-occurring psychiatric conditions, including anxiety, mood, and trauma- and stress-related disorders, at rates greater than in the general population [40, 47]. In addition, research on substance use disorders suggests that individuals with co-occurring substance use and psychiatric disorders tend to be more likely to experience withdrawal, and, among those who do experience withdrawal, it is usually of greater intensity and severity in the presence of a co-occurring mental health disorder (e.g., [1, 83]). However, the impact of both co-occurring substance use and psychiatric disorders on cannabis withdrawal is not well understood and is limited to a small number of empirical studies. Cannabis withdrawal is clearly evident in adult patients receiving residential detoxification from multiple drugs of abuse, including cannabis [49]. Compared to adult

outpatients without opioid dependence, adults with opioid dependence are more likely to report cannabis withdrawal-related sleep disturbances [82]. Similarly, adult inpatients with and without heroin dependence reported a comparable number of cannabis withdrawal symptoms, but analysis of individual items indicated that patients with heroin dependence experienced less irritability/anger/aggression, restlessness, and somatic complaints [19]. A study of patients in a residential detoxification unit in Australia showed that withdrawal severity was greater among those who had received treatment for mental health problems in the 6 months prior to admission, but secondary substance use was not associated with different withdrawal [31]. A robust cannabis withdrawal effect was observed in adult cannabis users with schizophrenia, with a majority of those reporting that they had taken some action, including resumed cannabis use, to mitigate withdrawal symptoms during past periods of abstinence [9]. In a sample of treatment-seeking adolescents, Greene et al. found no evidence of a relation between prospective assessments of cannabis withdrawal and psychiatric symptoms on percentage of days abstinent at follow-up [41]. At present, Schuster and colleagues addressed a significant gap in the literature by examining the impact of psychiatric comorbidity on cannabis withdrawal scores over time in a sample of non-treatment-seeking young adults [74]. Compared to individuals without a psychiatric diagnosis, individuals with a psychiatric diagnosis tended to experience greater cannabis withdrawal, but this finding was only evident during the first week of abstinence; groups reported comparable scores at subsequent time points.

Clinical Implications

A comprehensive understanding of the symptoms and severity of cannabis withdrawal has a series of important implications that are pertinent to the maintenance of daily cannabis use and the overall likelihood of achieving sustained abstinence.

Withdrawal as a Negative Reinforcer

It is well-established that drug use is motivated by basic reinforcement processes [35, 53]. From a negative reinforcement framework, cannabis withdrawal is known to elicit significant discomfort, and individuals frequently identify cannabis withdrawal as one of the major reasons listed as contributing to relapse following periods of cannabis abstinence [18, 23, 26, 59]. More recently, data acquired using ecological momentary assessment techniques have illustrated that cannabis self-administration is closely related in time to the report of cannabis withdrawal symptoms [10, 11].

Predictive Validity

While several studies have implicated cannabis withdrawal as a reason for returning to use after periods of abstinence, the reliability and significance of the association between cannabis withdrawal and treatment outcomes are not fully understood. Part of the difficulty here is that not all individuals entering in clinical trials are able to achieve abstinence, and those that do often quit at different times and for variable duration, which makes prospective evaluation of withdrawal during treatment difficult to systematically achieve. The most common approach has been to retrospectively evaluate the presence and severity of withdrawal among those who quit. The limitation of that approach is that the data is subject to recall and attribution biases. However, prospective data collection results in the inclusion of "withdrawal" assessments conducted in individuals when they are still using cannabis. This has been addressed in some studies by measuring withdrawal in a residential treatment setting.

In one study, cannabis users who had initiated a quit attempt in the past month indicated in a phone interview that withdrawal symptoms significantly contributed to relapse [18]. Greater than 50% of participants reported that aggression, anger, anxiety, craving, depressed mood, difficulty concentrating, irritability, restlessness, and sleep difficulty had contributed to failed quit attempts. In data obtained from two clinical trials conducted with treatment-seeking adolescents, cannabis withdrawal was predictive of a rapid relapse to cannabis dependence and more severe problems associated with cannabis use, but not cannabis use frequency posttreatment [20, 25]. In a placebo-controlled trial evaluating buspirone for cannabis dependence, McRae-Clark et al. found that participants who failed to report significant attenuation of cannabis withdrawal symptoms were less likely than others to achieve sustained abstinence confirmed by a negative urine sample during treatment [66]. A study of emerging adults receiving outpatient treatment demonstrated a trend that cannabis withdrawal predicted days to first lapse [30]. Gorelick et al. also found that non-treatment-seeking adults who met DSM-5 criteria for cannabis withdrawal had a shorter abstinence period during their most serious past quit attempt compared with individuals that did not report withdrawal [38].

In contrast to these findings, Arendt and colleagues found that cannabis withdrawal scores among individuals receiving inpatient or outpatient treatment were not predictive of subsequent relapse to cannabis use [6]. Similarly, a study of adolescents in outpatient treatment for cannabis use problems failed to find a significant relation between withdrawal and percentage of abstinent days at a 1-year follow-up [41]. However, the authors of that study noted that there was a moderating effect of whether or not the adolescents acknowledged having a problem with cannabis use at the outset of

treatment. Additionally, two recent clinical trials of pharmacotherapies for cannabis use disorder have shown significant reductions in cannabis withdrawal. The controlled trial of dronabinol failed to demonstrate an effect of the medication on cannabis use outcomes despite withdrawal attenuation [58], but the trial of gabapentin showed both a suppression of withdrawal and increased abstinence that was suggestive that withdrawal attenuation contributed toward the reduction in use [65]. These findings need to be replicated in larger follow-up trials.

To identify specific features of cannabis withdrawal that significantly predict relapse, Allsop et al. created and tested three separate models containing somatic variables, affective variables, and a third model that combined somatic and affective withdrawal variables [2]. Interestingly, only the somatic variables model significantly predicted relapse and inspection of individual variables included in the model indicated that physical tension was the only significant predictor variable. Overall, it appears that cannabis withdrawal is somewhat predictive of treatment outcomes, but there is variability in response across studies. Further, it remains to be determined whether withdrawal suppression is a viable mediator of cannabis use outcomes and, thus, an appropriate clinical target in developing novel treatments for CUD.

Conclusion

Cannabis withdrawal is a valid clinical syndrome that emerges following abrupt cessation of frequent cannabis use. Symptoms of cannabis withdrawal are predominantly behavioral and affective in nature and include irritability/anger/aggression, nervousness/anxiety, sleep difficulty (e.g., insomnia, strange or vivid dreams), decreased appetite or weight loss, restlessness, and depressed mood. Physical symptoms include abdominal/stomach pain, shakiness/tremors, sweating, fever, chills, or headache, but these are experienced less frequently [15, 43, 45, 55]. A consistent time course has been established; upon cessation, symptoms emerge within 24–48 h, reach peak intensity on days 2–5, and resolve within 2–3 weeks, though sleep difficulties may persist [15, 55]. Importantly, cannabis withdrawal produces significant discomfort and functional impairment [2], and work has also demonstrated that cannabis withdrawal is a significant factor that maintains regular use and reduces the likelihood of initiating a quit attempt [12, 14]. Compared with other drug withdrawal syndromes, the signs and symptoms of cannabis withdrawal are most comparable to the symptoms experienced during tobacco withdrawal. In contrast to the onset of withdrawal from tobacco, alcohol, and opioids, symptoms of cannabis withdrawal emerge and reach peak severity more gradually.

Efforts to determine the neurobiological underpinnings of cannabis reinforcement facilitated the identification of the endocannabinoid system. Basic science research has established that the endocannabinoid system serves as the primary biological mechanism of cannabis withdrawal. Data indicate that cannabis withdrawal is mediated by downregulation of the CB1 receptor and can be mitigated by administration of CB1 agonists. Demonstration of the neurobiological underpinnings and pharmacological specificity of cannabis withdrawal represented a critical step in establishing its validity and broad medical acceptance. Recent preclinical data also provide compelling evidence of a sexually dimorphic endocannabinoid system [46] that may explain the finding that, compared to males, females report more rapid development of cannabis use disorder and an increased number and severity of withdrawal symptoms [24, 48]. How fluctuating levels and degradation of the endogenous cannabinoids AEA and 2-AG impact cannabis withdrawal remains unknown and represents a focused area of research still in its infancy.

Akin to other validated drug withdrawal syndromes, variability in cannabis withdrawal between subjects is evident. Aside from the sex differences described above, there are studies that suggest longer durations of cannabis use, age, race, co-use of other substances, the presence of comorbid psychopathology, and heredity may influence subjective appraisals of cannabis withdrawal. However, retrospective and prospective studies of cannabis withdrawal have yielded equivocal results for most of these relations and represent areas that warrant additional research.

Establishing the validity and clinical significance of the cannabis withdrawal syndrome has several implications. Recognition of the cannabis withdrawal syndrome in the DSM-5 highlights the significance of the cannabis withdrawal syndrome, and validation of the signs and symptoms that characterize cannabis withdrawal is highly valuable for both clinicians and researchers and can help ensure diagnostic accuracy and inform the development of novel behavioral and pharmacological interventions. The validation and clinical significance of the cannabis withdrawal syndrome also have important public health considerations. Treatment admissions for cannabis have increased [72], and additionally, findings from recent population surveys have illustrated a sharp decrease in the general public's perception of the risk of harm from smoking cannabis ([8, 21]; see also [8]). Though the mechanisms that may contribute to the observed decline in the perceived risks associated with cannabis use are not fully understood, official recognition of a cannabis withdrawal syndrome may partly convey the consequences of long-term frequent use of cannabis.

Most studies that have evaluated the clinical importance of cannabis withdrawal indicate that the presence or severity of withdrawal is associated with cannabis use outcomes among those trying to quit. This has led to a number of efforts to develop pharmacotherapies as

adjuncts to the treatment of cannabis use disorder [7, 22, 39, 63, 80]. However, drawing accurate conclusions from research designed to evaluate the impact of cannabis withdrawal (i.e., symptoms, intensity, and severity) on treatment outcomes faces several challenges. Cannabis withdrawal is predominantly based on retrospective self-report questionnaires and susceptible to recall and attribution bias. Perhaps the best indication of the clinical importance of reducing cannabis withdrawal as a means to improve cannabis treatment outcomes was the trial by Mason and colleagues [65] in which gabapentin reduced withdrawal and increased abstinence. However, that was a relatively small clinical trial that requires replication, especially in light of the outcomes of reduced withdrawal in the absence of reduced cannabis use in the dronabinol trial conducted by Levin et al. [58]. To date, there has been no definitive study to demonstrate that attenuation of cannabis withdrawal mediates the likelihood of achieving sustained cannabis abstinence or prevention of relapse during a quit attempt.

Additional research is needed to fully determine the impact of cannabis withdrawal on the development and maintenance of CUD. In particular, there is a strong need to better understand individual differences in withdrawal expression and impact on clinical outcomes. Enhanced basic science research on the unique contributions of specific components of the endocannabinoid system may also better highlight the precise neurobiological mechanisms of specific cannabis withdrawal symptoms and may help to delineate the physiological mechanisms that account for the documented individual differences in the magnitude and duration of withdrawal observed in some studies. Studies evaluating the unique impact of specific withdrawal symptoms (e.g., anxiety, sleep disturbance) on clinical outcomes (e.g., abstinence initiation, relapse) would be beneficial in determining more targeted therapeutic approaches to treating cannabis use disorder. Finally, it is unclear whether individuals using cannabis for medicinal purposes are at the same risk of experiencing cannabis withdrawal upon cessation as those using cannabis for nonmedical purposes. Systematic evaluation of the rate, severity, and consequences of cannabis withdrawal in this population is urgently needed given the rapid growth in the number of individuals using cannabis for purported therapeutic purposes.

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Cannabis and Cannabinoid Intoxication and Toxicity

12

Ziva D. Cooper and Arthur Robin Williams

Technical Terms/Abbreviations

THC	Delta-9-tetrahydrocannabinol
SC	Synthetic cannabinoids

Introduction

The last 20 years has witnessed an explosion nationwide in legal access to the cannabis plant and cannabis-derived products for both medical and recreational purposes [68]. As of November 2016, 29 states and Washington DC allowed for medical cannabis access of some kind for patients 18+ years of age, and 8 states and Washington DC had legalized recreational use for adults 21 years or older. With greater availability of legal cannabis, rates of use and heavy use (i.e., daily or near-daily use) have increased dramatically among adults [11, 19, 66]. However there is great variation among states in how they regulate access to cannabis and cannabis-derived products (such as tinctures, vapes, and pills derived from plant extracts) that may impact patterns of use and effects at the population level [5, 45, 67]. Additionally, more than a dozen states have now legalized access to cannabidiol-based products (cannabidiol, or CBD, is the other predominant cannabinoid in addition to THC in cannabis), mostly for research purposes (i.e., in university settings to investigate potential uses of CBD for epilepsy). Given that expanded access to cannabis and its derivatives has often been promulgated by passionate public support, research on the implications of fast-moving legal reforms and state regulation on patterns of use, intoxication, and downstream complications greatly lags real-world consequences [46].

While there is no legal access to recreationally used synthetic cannabinoids, products that are intended to mimic the effects of THC (i.e., Spice, K2), there have been several notable epidemics of synthetic cannabinoids across the United States [31]. Legal and policy-based efforts to constrain access to these synthetic and often dangerous compounds have not kept pace with the emergence of new compounds on the black market. Emphasis throughout the chapter will be placed on how intoxication, overdose, and clinical management for synthetics may differ from that of (non-synthetic) cannabis and cannabis-derived products.

Cannabis Availability Is Increasing

With expanded legal access to medical and recreational cannabis, there has been tremendous concern that increased availability could lead to increases in adolescent use. To date, these concerns have been unfounded, likely because adolescents have historically had easier access to cannabis than adults. Paradoxically then, studies have shown that the greatest increases in use of cannabis have been among adults and older adults [19]. Further, with greater rates of heavy use among adults [33], once rare clinical presentations (such as cyclic vomiting syndrome) are becoming more common, and there is growing concern about public hazards from public intoxication such as drugged driving [18]. One impact of expanded legal access to cannabis and especially cannabis-derived products, such as gummy bears, chocolate squares, and other items that resemble candy, is the increasing rate of child poisonings [29]. Both poison control centers and emergency departments in affected states have been reporting historically high rates of pediatric cannabis-related presentations suggesting one unintended consequence of expanded legal access for adults has been increased inadvertent access for children [64].

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Emerging Trends in Use and Product Type

Alongside legislative changes in the United States related to access and use of cannabis, trends in use patterns and cannabis-related products are emerging (Table 12.1). These trends include high-strength cannabis and cannabis-derived products that are produced for smoking (i.e., wax, dabs), vaporizing, (cannabis extracts), and ingesting orally (edibles). The strength of cannabis and cannabis-derived products is defined by the concentration of delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of the cannabis plant [34]. The average strength of seized (black market) cannabis has increased from about 4% THC to 12% between 1995 and 2014 [16], and the average strength of cannabis available from legal cannabis retail locations often surpasses 20% [53]. High-strength products including extracts for inhalation, sold as concentrates (i.e., wax and shatter) and resin (i.e., hash), are reported to be over 65% THC [53]. Edibles, which are increasing in popularity [7], are sold in units that contain multiple doses (usually around 10 mg THC) [6]. These products are at high risk for eliciting an adverse reaction, unintentional over-intoxication, and toxicity in the pediatric population. Edibles are often visibly appealing and produced as baked goods or candy, making them enticing to children. Furthermore, because of the delayed onset of effects with the oral route of administration, people frequently eat more units without taking into account delayed effects [6], resulting in a long-lasting, over-intoxication. An additional variable related to edibles that make them high-risk products is that the labeling is frequently inaccurate, with some products containing much more THC than described on the package [57].

Overview of Chapter Content

The information described in this chapter is geared toward giving the reader an understanding of the issues related to cannabis and cannabinoid intoxication, accidental overdose, and toxicity. Given the increase in cannabis availability, emerging trends in available products, and the widespread emergence of synthetic cannabinoid use, awareness of signs and symptoms of intoxication, overdose, and clinical management is becoming increasingly relevant to psychiatric and general medical providers. The prevalence of poisonings and overdose will be described to provide a scope of the issue. Behavioral and physical signs and symptoms of intoxication and toxicity will be discussed. Lastly, data pertaining to established and exploratory treatment for intoxication and toxicity will be highlighted, and policy changes that may help build awareness of potential cannabis-related harms and prevent unintended population-level outcomes will be mentioned.

Table 12.1 Emerging risks

Cannabinoid	Emerging trend with potential for increased risk of adverse effects
Cannabis and cannabis-derived products	Increase strength of smoked cannabis defined by % THC content
	High THC cannabis extracts (dabs, shatter)
	Increases access and diversity of edible cannabis products
Synthetic cannabinoid products	Products comprising various cannabinoid receptor 1 (CB1) agonists with high receptor affinity and efficacy

Rates of Overdose and At-Risk Populations

Rates of calls to poison control centers and hospital presentations due to cannabis exposure vary across ages, states with legal cannabis regulation, and cannabis product. Incidents of accidental overdose that are reported appear to be most frequent in younger pediatric population (<7 years of age) and are usually due to ingestion of oral products [44]. Furthermore, rates of cannabis overdose incidents are highest in states with permissive cannabis laws [10]. However, it should be noted that these rates are based on patients reporting over-intoxication and do not take into account incidents that were not called into the poison control centers or those that did not prompt visit to the emergency room.

Rates of Cannabis-Related Overdose/Calls to Poison Control Centers over Time

According to data published by the American Association of Poison Control Centers (AAPCC), the number of calls to poison control centers related to cannabis products has been increasing consistently. The most recent report from 2015 documents that cannabis was mentioned in over 6500 cases involved with other substances and over 2400 cases involving only cannabis [42]. This number exceeded calls in 2014 when over 5600 cases mentioned cases including cannabis and other drugs and 2000 cases involving only cannabis. The number is also higher than data from 2013, which documents 5000 case mentions involving cannabis and other drugs and 1500 cases involving only cannabis [40–42]. Although the largest group of cannabis-related calls consisted of those 20 years and older (~40%), children under 5 years of age have represented approximately 17% of those effected by single-substance exposures to cannabis. Outside of the United States, other countries have also documented rates of pediatric cannabis toxicity including France [12, 30]. With the increased number of calls to AAPCC related to single-substance exposures to cannabis, the rates of *unintentional*

exposure have increased from 25.7% in 2013 to 28.8% in 2015, as have the percent of callers treated in a health care facility (68 to 72.4%) and outcomes defined as "major" or "death" (1.1% in 2013 to 2.1% in 2015). This upward trend in cannabis-related exposures over the last few years that have necessitated medical care demonstrates a significant need to determine best clinical practices to treat adverse effects of exposure.

Rates of Cannabis-Related Overdose/Calls to Poison Control Centers as a Function of State Cannabis Laws

Pediatric unintentional cannabis exposure occurs at a higher rate in states with legal cannabis regulation relative to states without legal access to cannabis [10]. Furthermore, data support increases in rates of adverse effects of cannabis exposure in states before and after laws permitting cannabis use came into effect. For instance, between 2005 and 2009 in Colorado, no cases of unintentional cannabis exposure were reported in the pediatric population at a state children's hospital, yet between 2009 and 2013, a time that coincided with more lax regulations, the percent of pediatric patients admitted for cannabis exposures was 2.4% of the population admitted for any unintentional drug ingestion [64]. When comparing the 2 years before and after legalization of cannabis for adult use in Colorado, the number of cannabis-related visit to the emergency department increased (from 4.3 to 6.4 per 1000 visits), as did calls to Colorado poison centers related to cannabis exposure (from 0.9 in 1000 calls to the centers in 2012–2013 to 2.3 in 2014–2015) [65]. Data analyzed from the National Poison Data System between 2000 and 2013 confirmed an increase in annual rates of exposure among the pediatric population across the country, with an increase of 147.5% between 2006 and 201; in states that had legalized cannabis for medical purposes before 2000, cannabis-related exposures increased by nearly 610%. Unintentional cannabis toxicity in this population has been documented to be specifically due to ingestion of cannabis or a cannabis product [44]. The annual rate of calls to poison control centers was also 2.8 times higher in states with legal medical cannabis laws enacted prior to 2000 relative to states without legal cannabis (as of 2013). Between 2004 and 2011, emergency department visit rates related to cannabis-only exposures increased from 51 to 73 per 100,000 visits per year; ED visits related to cannabis-polydrug use also increased from 63 to 100 per 100,000 visits during the same time period. The age group that exhibited the largest increase in cannabis-only ED visit rates was adolescents aged 12–17 years [71]. Australia has also witnessed an increase in cannabis-related presentations to emergency health services in the adult population since 2000. Between 2000 and 2010, rates of cannabis-related treatments were documented to be 0.6 per 100,000 emergency visits per year. Between the years of 2010 and 2013, this number increased to 5.5 per 100,000 visits per year [25].

At-Risk Populations for Cannabis Toxicity

As mentioned above, the population that appears to be at greatest risk for unintentional cannabis exposure is the pediatric population. Although there are no epidemiological reports of cannabis toxicity in older population, case reports have brought the issue to light with 12 patients, 59 +/− 11 years of age, requiring emergency care after consuming cannabis products. Primary symptoms, with exposure to much lower doses than those affecting younger adults, included vomiting, difficulty walking, hypothermia, dizziness, and visual hallucinations. Patients were treated with supportive therapy with saline infusions and potassium supplements. Two patients were admitted into intensive care for profound decreases in consciousness and monitored until consciousness was regained about 24 h after admission. The authors note that these patients were not experienced cannabis users, which most likely contributed to the adverse effects [72].

Synthetic Cannabinoid Rates of Overdose and At-Risk Population

Synthetic cannabinoid (SC) products, sometimes referred to as popularly used names "Spice" or "K2," were first identified in the United States in 2008. The primary chemical constituents of these products are cannabinoid 1 (CB1) receptor agonists, similar to THC. Yet these compounds have higher affinity and efficacy at the receptor relative to THC, which is hypothesized to contribute to some of their adverse effects (Table 12.1**:** [13]). SC products were initially used as a legal alternative to cannabis, available at local convenience shop at a lower cost than cannabis. Their use was not detected in urine toxicology screens, which added to their appeal. In 2011, poison control centers received 240% more phone calls associated with synthetic cannabinoid exposure relative to 2010, raising awareness to the immediate hazards of these drugs [1]. Since then, the Drug Enforcement Administration actively sought to curb production and sales of these products by classifying several chemical structural classes of cannabinoid as Schedule 1 (i.e., US Drug Enforcement Administration, [61–63]), yet new compounds continue to emerge to circumvent these bans. Calls to poison control centers have indeed decreased with only 2695 calls reported in 2016, a decrease from 6.968 class in 2011 [2]; however, there are occasional "outbreaks" in US regions ascribed to

certain synthetic cannabinoid products and compounds that elicit a severe constellation of adverse reactions after use that lead in an influx of calls to poison control centers and emergency room visits [13]. For instance, within a 9-month period between 2015 and 2016, 1351 patients required emergency care in Anchorage, Alaska [54]. During that year, Mississippi Poison Control Centers (MPCC) received over 700 synthetic cannabis-related calls in a single month [26], and in New York, Emergency Medical Services were required to respond to adverse reactions due to synthetic cannabinoid use in 33 patients in a single day [3]. These patients are typically male, and a significant percentage is classified as homeless with pre-existing psychiatric conditions (i.e., [3, 32, 54]). The overwhelming majority of exposure cases are reported to be due to recreational drug abuse, rather than to unintentional exposure [38].

Signs and Symptoms of Intoxication

Intoxication: Cannabis and Cannabis-Derived Products

Cannabis and cannabis-derived products when used recreationally cause predictable intoxidromes marked by effects such as relaxation and anxiolysis, euphoria, altered time (i.e., slowed) and sensory (i.e., intensified) perception, hyperfocused awareness of external stimuli, and increased appetite [17]. Signs and symptoms of intoxication typically manifest within 2 h of use, coinciding with peak plasma levels of THC [15]. Although these effects are often desired by recreational users, they may be unpleasant for individuals who report discomfort or anxiety when using cannabis. Related to the aforementioned effects, common unwanted changes may include impairment in coordination and motor skills, memory (anterograde) and learning difficulties, and injected or reddened conjunctiva (see Table 12.2A). Given that the relative strength of THC in cannabis has increased dramatically in the past two decades (now upward of 12%) [16, 35, 51], users are more likely to consume relatively higher doses of THC, which can cause more dramatic effects during intoxication.

Using large amounts (approximately 20 mg + THC equivalent), especially among individuals with low or no tolerance, can lead to symptoms of anxiety and panic, symptoms of psychosis such as paranoia, derealization, depersonalization, illusions or hallucinations (auditory and/or visual), and delirium [58]. For individuals who develop psychosis, symptoms may persist for a week or longer [15]. Inadvertent consumption of high-dose cannabis is often associated with using edible formulations (i.e., candies, brownies, "cannabutter") that are notoriously mislabeled or inaccurately dosed [57]. Additionally, there is great variation across individuals in the absorption and clearance of cannabis and its derivatives through the gastrointestinal tract, which makes oral dosing unpredictable. As the legal commercialization of cannabis expands for both medical and recreational users, it brings new formulations of cannabis and new users who may be less experienced with oral dosing and more susceptible to complications from intoxication.

Intoxication: Synthetic Cannabinoids

Unlike the wealth of knowledgerelated to adverse effects of cannabis obtained from controlled studies of acute intoxica-

Table 12.2A Signs and symptoms of complications from cannabis intoxication in adults[a]

Cannabis and cannabis-derived products[a]	*Psychiatric*	Mild: "abnormal" behavior and/or appearance, inappropriate affect, depressed mood, hallucinations, bizarre behavior, dangerous behavior toward others
		Moderate: impaired memory, expansive or euphoric mood, disorganized thought process, suicidal or dangerous behaviors toward self
		Severe: delusions, impaired judgment
	Physiologic	Mild: pupil constriction, nystagmus, headache, tachypnea, tremor, urinary retention, ataxia, sedation, lethargy
		Moderate: conjunctival injection/redness, orthostatic hypotension, increased heart rate, palpitations, arrhythmia, decreased blood pressure, decreased coordination, increased appetite
Synthetic cannabinoids and cannabinomimetics[b]	*Psychiatric*	Mild: dizziness, altered mental status
		Moderate: memory impairment, paranoia, hallucinations
		Severe: delusions, impaired judgment, agitation, persistent psychosis, violence toward self and others including self-injurious behaviors, suicide, homicide
	Physiologic	Mild: increase appetite, fatigue, headache, sedation, lethargy
		Moderate: nausea, vomiting, tachycardia, hypertension, orthostatic hypotension, arrhythmia, respiratory depression, pneumonitis, ataxia
		Severe: acute ischemic stroke, seizures, acute myocardial infarction, rhabdomyolysis, renal failure, overdose-related mortality

[a]Adapted from Principles of Addiction Medicine, 4th Edition (pp. 613–614), Crippa et al. [15]; Volkow et al. [58]
[b]Adapted from [31]

tion, most of what is known regarding synthetic cannabinoid intoxication and adverse effects is either from self-report surveys or from exposure cases that are dealt with in emergency department settings. Because the content of synthetic cannabinoid products varies in chemical constituents and concentration of these constituents, their effects are often unpredictable. Unless the patient endorses synthetic cannabinoid use, it can be difficult to attribute intoxication to their use since they do not show up in commonly used urine toxicology screens. Furthermore, new compounds that appear on the market can elicit different symptoms of intoxication than those documented with earlier compounds on the black market. Differences between synthetic cannabinoid products and their effects are thought to be due to differences in their pharmacokinetic and pharmacodynamic properties [13]. However, common trends in signs of intoxication and toxic effects have emerged over the years.

Below we highlight the common psychiatric and physiological signs of intoxication and toxicity (see also Table 12.2A). The most frequently reported adverse psychiatric effects include psychosis [36, 38] and anxiety Zawilska et al. [70]. Agitation, irritability, and paranoia [14, 38], lack of responsiveness and lethargy [3, 49], and hallucinations [13, 14, 49] are also common. Severe physiological effects include respiratory depression [4, 23]; nephrotoxicity [8]; gastrointestinal disruptions including hyperemesis, nausea, and abdominal pain [9, 21, 49, 52, 59]; rhabdomyolysis; hyperthermia [55]; seizures [28, 38]; acute cerebral ischemia [56]; and cardiotoxicity including dysrhythmia [37, 69]. Less severe symptoms include tachycardia, bradycardia, hypotension, and arrhythmias [27, 38]. Because the chemical composition of synthetic cannabinoid products varies with respect to compounds and their concentration, the presentation of these symptoms and their severity and duration vary as well.

Differential Diagnosis

In addition to urine toxicology or methods to determine recent drug ingestion, determining whether a presentation (i.e., in the emergency department) is related in part or in full to recent drug use often requires extended observation and ideally additional collateral information confirming the patient's history. Otherwise, acutely intoxicated individuals with anxiety or panic symptoms may be difficult to distinguish from primary anxiety disorders. Similarly, psychosis during acute intoxication can mimic primary psychotic disorders such as delusional disorders and schizophrenia. Visual hallucinations however are more often associated with drug intoxication (due to cannabis, stimulants, hallucinogens, etc.) rather than a primary psychotic disorder and resolve following drug cessation [48].

Although many cannabis and synthetic cannabinoid users may not regularly combine other drugs of abuse, it is important for clinicians to be aware that some users smoke cannabis "wet" or dipped in other drugs such as inhalants or sprinkled with phencyclidine (PCP). Co-usage of cannabis and other psychotogenic substances may complicate clinical presentations and the time course of symptom resolution.

Patients with a history of psychosis or risk factors (i.e., genetic loading, family history, early life trauma, odd behaviors in childhood) for schizophrenia are predisposed to developing more dramatic and protracted psychosis following use of cannabis and synthetic cannabinoids than individuals in the general population [39]. It is important to identify what may be transient psychotic symptoms (i.e., paranoia visual hallucinations) due to active intoxication compared to new-onset psychosis or reactivated symptoms (i.e., ego-dystonic command auditory hallucinations) that require ongoing treatment beyond cessation of cannabis alone.

Treating Overdose and Complications

Cannabis

Cannabis intoxication historically has been relatively mild and self-limited requiring only supportive care (i.e., place patient in a quiet environment with supportive reassurance and hydration). However heavier usage can lead to overdose and toxicity resulting in more complicated clinical presentations benefiting from active pharmacologic management and symptom-targeted therapy (see Table 12.3). Pharmacological approaches to treating cannabis intoxication or overdose most often include the use of sedative-hypnotics such as clonazepam or lorazepam. These may be best suited for patients with anxiety, panic, and restlessness. Antipsychotics can also be used for treatment, especially for patients with more severe psychotic symptoms such as paranoia, delusions, hallucinations, or extreme behavioral dysregulation. Generally c-generation agents such as risperidone or olanzapine are preferred [15, 48]. Although less commonly used, beta-blockers have also been shown to reduce the severity of cardiovascular effects such as tachycardia and palpitations [15].

For patients with schizophrenia or at risk for psychosis, use of cannabis may be destabilizing to otherwise controlled symptoms. In these cases, patients may remain decompensated from baseline despite cessation of active cannabis use. Initiation, maintenance, or increased dosing of standing antipsychotics may be required to adequately manage psychosis.

Cannabinoid hyperemesis syndrome (cyclic vomiting syndrome) has become a more widely recognized clinical entity in the past few years given increased rates of heavy use

of high-strength cannabis. Patients may report excessive use of "hot showers" which can provide symptom relief temporarily [47]. Acute presentations may or may not involve intoxication on presentation and often include intractable nausea and vomiting lasting days to months and may be especially difficult to control among patients with comorbid or poorly controlled migraine, psychiatric, or opioid use disorders [18]. Controlled studies are few and case reports are mixed on effective treatment [47]. Acute treatment often relies on a sedative hypnotic, such as lorazepam, and antipsychotics with an antiemetic, such as promethazine or ondansetron, for breakthrough nausea. Some patients further benefit from non-opioid pain medications such as nonsteroidal anti-inflammatories when their presentation is accompanied by abdominal pain. Ongoing treatment to prevent recurrent episodes may include long-term use of tricyclic antidepressants but otherwise primarily relies on avoidance of known triggers including emotional stress, chronic sleep deprivation, and prolonged fasting in addition to avoiding cannabis consumption [18].

Unlike adults, children, especially young children under 2 years of age, are susceptible to life-threatening encephalopathy, respiratory insufficiency, arrhythmia, and coma with cannabis ingestion (see Table 12.2B) [12, 29, 64]. Prior to widespread legalization and the commercialization of edibles and high-strength waxes and resins, pediatric presentations to the emergency department were virtually nonexistent. Increasingly, poison control centers and emergency departments (i.e., in states such as Colorado) report presentations of children with altered sensorium, ataxia or hypotonia, and at times coma resulting from inadvertent cannabis ingestion, at times unbeknownst to caregivers but determined through urine toxicology [29]. Children on presentation are often hemodynamically stable and may present with non-specific signs, complicating diagnosis.

Table 12.2B Signs and symptoms of cannabis intoxication in children and treatment options

Symptom[a]	Treatment
Altered mental status	Supportive care, monitoring
Mydriasis	Supportive care
Tachycardia[a]	Supportive care, monitoring
Dystonia, hypotonia, catatonia, ataxia	Supportive care, monitoring, fluid management
Respiratory depression/ insufficiency	Airway support, intubation, fluid management, ICU admission
Arrhythmia	Antiarrhythmics, continuous monitoring of vital signs, ICU admission
Seizure	Benzodiazepines, supportive care, close monitoring
Coma	Intensive monitoring and support in ICU, consider flumazenil
	It is additionally recommended that providers screen caregivers for possible abuse or neglect in the home that may be associated with pediatric ingestion

[a]Children presenting with acute cannabis intoxication are often hemodynamically stable with non-specific systemic symptoms of encephalopathy frequently prompting a broad differential diagnosis and work-up until cannabis ingestion has been confirmed by caregiver report and/or urine toxicology. Content derived from Wang et al. [64]; Lavi et al. [29]; Claudet et al. [12].

Synthetic Cannabinoids

Treatment of overdose from synthetic cannabinoids can be much more challenging especially when complicated by persistent agitation and violence. Importantly, some drugs believed by users to be synthetic "cannabinoids" can contain cathinones, stimulants, or adulterated with such agents which can complicate clinical presentations and symptoms response to treatment [31]. Unless symptoms are severe, treatment for synthetic cannabinoid toxicity usually entails supportive care, including supplemental oxygen, cardiac monitoring, intravenous fluids to address fluid imbalance, and electrolyte depletion ([20, 49]; Table 12.3). For psychiatric disturbances including agitation, hostility, and anxiety, patients are usually treated with benzodiazepines [20, 38]. Benzodiazepines are the most common pharmacologic treatment followed by antipsychotics [38], which are usually administered for patients who exhibit psychosis, as well as for agitation and mania [43, 55, 60]. Antiemetics are administrated to address vomiting and nausea [49]. Seizures are treated with benzodi-

Table 12.3 Common treatments for intoxication and overdose from cannabinoids and synthetic products

Drug	Treatment
Cannabis and cannabis-derived products	*Non-pharmacologic* Supportive care with hydration, monitoring of vitals Place patient in quiet room Provide supportive reassurance *Pharmacologic* Sedative-hypnotics (clonazepam, lorazepam, oxazepam) Antipsychotics, typically second generation (risperidone, quetiapine) Non-benzodiazepine anxiolytics such as hydroxyzine
Synthetic cannabinoid products	*Mild cases* may benefit from supportive care alone or typical management for cannabis intoxication *Severe cases* Repeat administration of high-potency antipsychotics (i.e., haloperidol) Sedating antipsychotics when agitation is dangerous (i.e., chlorpromazine or olanzapine) Sedative-hypnotics (clonazepam, lorazepam, oxazepam) Consider behavioral isolation precautions

azepines [50]. Cases with severe toxicity require hospital admission, sometimes to the intensive care unit. Respiratory depression has been reported to necessitate endotracheal intubation; recovery of normal respiration was observed within 24 h [4]. Severe hypotension has been reported to require the use of vasopressors [38].

Discussion/Conclusion

Significance of the Issue and Potential Novel Treatments to Address Intoxication

Cannabis and synthetic cannabinoid toxicity is an immediate public health issue. Cases of drug abuse and unintentional exposure related to cannabis and cannabis-derived products are increasing across the country and specifically in states that have legalized cannabis for medical and recreational purposes. As laws permit greater access and use, and as cannabis products continue to diversify, rates of unintentional intoxication are predicted to increase. While cannabis toxicity is usually mild and resolves soon after exposure, there have been severe cases reported that require medical attention. The pediatric population is an age group that's of high risk for unintentional exposure and most severe outcomes. With increases in rates of cannabis and synthetic cannabinoid toxicity, potential therapeutics to address severe effects are urgently needed. In addition to the common therapeutics used that target specifically symptomology, agents that work directly to reverse cannabinoid toxicity rapidly will be critical for care. Similar to Narcan, an opioid antagonist that reverses an opioid overdose, a CB1 receptor antagonist has been postulated to be an ideal agent in treating cannabinoid toxicity. While a clinically tested CB1 receptor antagonist exists (rimonabant), it is not available for clinical use at this time. However, studies assessing its effects on smoked cannabis's cardiovascular and subjective effects have demonstrated promise in its ability to significantly decrease cannabinoid effects when administrated as a pretreatment [22]. As of yet, its potential effectiveness when administered after cannabinoid administration, as would be the scenario when treating cannabis and cannabinoid overdose, is unknown. Because synthetic cannabinoid products contain high-efficacy CB1 receptor agonists, administration of a partial CB1 receptor agonist, like THC, may reverse their toxic effects. Finally, there is some indication in the literature that administration of the mu-opioid antagonist, naloxone, may reverse synthetic cannabinoid toxicity [24]. Awareness of cannabis toxicity, and knowledge of common signs and symptoms of toxicity, is the first step to identifying the issue. In the absence of novel pharmacotherapies to aid reversal of cannabis and cannabinoid toxicity, understanding the most effective treatment strategies to respond to overdose symptoms is critical.

Role of Policy in Addressing the Increase in Overdose.

Following high-profile deaths from cannabis-based edibles and complications after early recreational sales, policy makers have had to respond quickly and devise ways to safeguard against unintentional overdose. Some of these policies include (1) enhancing and verifying labeling of contents, (2) requiring child-proof packaging, and (3) requiring warning labels. Additionally, some states have set limits on allowable THC content, especially in edibles. Subsequent to media coverage of unintentional cannabis overdoses in Colorado, the state required recreational dispensaries to reduce the maximum amount of THC in an individual piece to no more than 10 mg. Similarly, the state of New York designed medical cannabis program regulations that disallow a single "dose" of cannabis-derived products (whole plant cannabis is not allowed to be dispensed in New York medical dispensaries) from containing more than 10 mg of THC [66]. Given the rapidly changing landscape of cannabis products and regulation, it is unclear how successful these interventions may prove in reducing harm from broader access to cannabis.

Key Points

- Expanded access to medical and recreational cannabis throughout much of the nation has led to increased rates of emergency room and clinical presentations of cannabis intoxication.
- Intoxication with synthetic cannabinoids is often more severe with behavioral dysregulation and can be refractory to traditional treatments.
- Pediatric ingestion of cannabis and related toxicity can lead to life-threatening encephalopathy and coma.
- Policies such as those requiring testing and accurate labeling of cannabis products, child-proof packaging, and limits on total THC in servings may help reduce complications from cannabis intoxication.

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Psychiatric Comorbidity of Cannabis Use Disorder

13

David A. Gorelick

Introduction

Cannabis use disorder (CUD) is among the most prevalent psychoactive substance use disorders (SUDs), with an estimated 13.1 million individuals worldwide having moderate-severe CUD (cannabis dependence in DSM-IV terms) in 2010 [1]. In the United States, an estimated 4.0 million community-dwelling residents had current (past-year) CUD in 2015, a prevalence rate of 1.5% [2].

Therefore, it is not surprising that CUD often co-occurs with other non-SUD psychiatric disorders [3]. For example, a 2007 nationally representative survey of 8,841 community-dwelling Australians 16–85 years old (2007 National Survey of Mental Health and Wellbeing [NSMHW]) found that 69.8% (standard error [SE] 6.5%) of respondents with current (past 12-month) CUD also had psychiatric comorbidity (affective [major depression, dysthymia, bipolar], anxiety [panic, agoraphobia, social phobia, generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder], and/or alcohol use disorder), compared with 37.8% (SE 3.5) of current cannabis users without CUD and 15.5% (SE 0.5) of current nonusers of cannabis [4]. The odds ratio (OR) for having any comorbid disorder was 3.8 (95% confidence interval [CI] 1.9–7.6) for current cannabis users with CUD vs. current users without CUD and 0.3 (95% CI 0.2–0.4) for current nonusers vs. current users without CUD [4]. A study of 15.1 million adult (18–65 years old) admissions to US non-federal, acute care community general hospitals between 2007 and 2011 (Nationwide Inpatient Sample [NIS] of the Healthcare Cost and Utilization Project [HCUP]) found that 62.05% (95% CI 60.66–63.43) of the 65,767 inpatients with CUD as their only diagnosed SUD also had another non-SUD psychiatric diagnosis (mood, anxiety, psychotic, adjustment, impulse control, personality, or attention-deficit disorder), compared with 27.28% (95% CI 26.90–27.66) of the 14.7 million inpatients without a CUD diagnosis [5]. A retrospective record review of all 1,814,830 patients admitted to 458 hospitals in New South Wales (NSW), Australia, between July 1, 2006, and June 30, 2007, identified 8,669 (5%) patients with a diagnosis of current CUD, of whom 53.8% had another major psychiatric diagnosis (major depressive disorder, bipolar disorder, anxiety disorder, schizophrenia, personality disorder, or "severe stress disorder"), compared with a 4.2% prevalence of these psychiatric disorders among all patients (OR 17.2, 95% CI 17.4–19.0) [6]. A study of 837 outpatients at Madrid mental health clinics found a 66.2% prevalence of current psychiatric comorbidity among the 135 outpatients with current CUD [7].

Whether this comorbidity is due to a direct causal relationship between disorders (in either direction), to the chance co-occurrence of two common disorders, or to the presence of antecedent risk factors that promote the development of both disorders is often unclear. Few epidemiological studies provide information that might allow causal inference, e.g., odds ratios for occurrence compared to a relevant reference group that might isolate the influence of CUD itself, such as cannabis users without CUD. Even fewer studies adjust the ORs to account for likely confounding risk factors, e.g., other substance use or SUDs and sociodemographic characteristics. The temporal order of onset of the two disorders provides clinically useful information (e.g., distinguishing between primary and secondary disorders), but this information is rarely available from large-scale epidemiological studies. Genetic and twin studies (e.g., comparing concordance for comorbidity in monozygotic and dizygotic twin pairs) might also be informative, but such studies almost always focus on cannabis use, rather than CUD [8].

CUD psychiatric comorbidity is clinically relevant because its presence is often associated with a poorer prognosis for CUD, the other psychiatric disorder, or both [3]. Clinically significant adverse consequences, such as poor treatment adherence and retention, more severe symptoms, greater functional disability, longer duration of active illness, more frequent occurrence of acute exacerbations, and/or greater rates

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of hospitalization, have been shown for bipolar disorder [9–13], depression [14], PTSD [15], and schizophrenia [16, 17].

This chapter reviews the epidemiology and treatment of CUD occurring with comorbid psychiatric disorders (except for other SUDs). For epidemiologic data, we focus on recent large-scale, community-based epidemiological surveys, as these provide the most scientifically rigorous data. The majority of such studies are cross-sectional and so do not provide evidence regarding the causal relationship between the two comorbid disorders. When available, we also present data from large-scale, prospective longitudinal studies which provide information about the incidence of comorbid disorders over a defined period of time. We present data on current, rather than lifetime, diagnoses to minimize the influence of recall bias on findings. We distinguish epidemiologic studies along two dimensions. First, do they report prevalence of the psychiatric disorder among individuals with CUD or prevalence of CUD among individuals with the psychiatric disorder? Second, are study subjects selected because they live in the community (and, ideally, are selected to be representative of everyone living in that community), regardless of treatment or treatment-seeking status, or are subjects selected because they are in treatment or seeking treatment (i.e., clinical populations)? The latter groups are likely to be enriched with individuals who have comorbid (i.e., two or more) disorders because those with multiple disorders are more likely to be in treatment (the so-called Berkson's bias or paradox) [18]. For treatment data, we focus on controlled clinical trials in which the majority of participants have diagnosed CUD and another specific psychiatric disorder.

This chapter does not cover cannabis use (i.e., without CUD) in the context of other psychiatric disorders, a topic on which there is substantial published literature. CUD comorbidity with schizophrenia (i.e., non-affective psychosis) is covered only briefly, as this topic is dealt with in more detail in the chapter by Drs. Tikka and D'Souza.

Mood Disorders

Epidemiology

Several nationally representative, cross-sectional epidemiological studies suggest substantial bidirectional comorbidity between CUD and mood or affective disorders (e.g., depression, dysthymia, bipolar). A 2012–2013 nationally representative survey of 36,309 non-institutionalized US adults (National Epidemiologic Survey on Alcohol and Related Conditions [NESARC]-III) found a 7.3% (SE 0.51%) prevalence of current (past 12-month) CUD among respondents with any current mood disorder (major depressive disorder, persistent depression, or bipolar disorder), compared with 2.5% in the general population [19]. The adjusted odds ratio (aOR) for current CUD among respondents with current mood disorder (compared to those without a current psychiatric disorder) was 3.8 (adjusted for sociodemographic characteristics, 95% CI 3.10–4.56). Viewing comorbidity from the opposite direction, the NESARC-III study found a 33.3% (SE 2.76%) prevalence (aOR 1.9 [adjusted for sociodemographic characteristics and other psychiatric disorders], 95% CI 1.34–2.64) of any current mood disorder among men with current CUD and 48.9% (3.46%) prevalence (aOR 1.5, 95% CI 1.05–2.23) among women [20]. The US NIS study found that 41.00% (95% CI 39.94–42.08) of adults hospitalized between 2007 and 2011 with CUD as their only SUD diagnosis also had a mood disorder diagnosis, compared with 19.49% (95% CI 19.18–19.80) of inpatients without a CUD diagnosis [5] . The 2007 Australian NSMHW found a similarly high rate of comorbidity: the prevalence of any current affective disorder (major depressive disorder, dysthymia, bipolar) was 36.9% (SE 8.1%) among respondents with current CUD, compared with 5.6% (0.3%) among current nonusers of cannabis and 12.5% (2.2%) among current cannabis users without current CUD [4]. The OR for having a comorbid affective disorder among respondents with current CUD, compared to current cannabis users without current CUD, was 3.0 (95% CI 1.4–6.6).

A similar finding of substantial comorbidity was found in a national registry study of 22,615 patients who entered treatment for a SUD in a publicly funded treatment facility in Chile between 2007 and 2013 [21]. Among the 1,265 patients with CUD as their only current illicit SUD, 13.2% (95% CI 11.4–15.2) had a current affective disorder (aOR 1.58 [adjusted for sociodemographic characteristics and alcohol use], 95% CI 1.30–1.92), compared to the 9.3% (95% CI 8.7–9.9) prevalence among the 9,526 patients with cocaine as their only current illicit SUD. The 11,824 patients with comorbid CUD and cocaine use disorder also had a significantly lower 8.7% (95% CI 8.2–9.2) prevalence of current affective disorder (aOR 1.07, 95% CI 0.96–1.12) compared to patients with cocaine use disorder only.

Mood disorders are associated with the development of CUD by cannabis users. A secondary analysis of data collected in the 2001–2002 NESARC study from a representative sample of 43,093 non-institutionalized US adults found that lifetime cannabis users with a mood disorder were significantly more likely to have CUD than were lifetime users without any psychiatric disorder (aOR 3.9 [adjusted for sociodemographic characteristics], 95% CI 2.8–5.3) [22].

Depression

Epidemiology

Large-scale, nationally representative epidemiological surveys of community-dwelling adults in several countries show

substantial comorbidity between CUD and depression. The 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with a current depressive disorder to be 6.2% (SE 0.49%) for major depressive disorder (aOR 2.8, 95% CI 2.33–3.41) and 7.8% (1.11%) for persistent depression [19]. A nationally representative survey of 39,133 non-institutionalized US adults (2011 National Survey on Drug Use and Health [NSDUH]) found a 4.11% (95% CI 3.15–5.08) prevalence of current CUD among respondents with current major depressive episode, compared with a 1.18% (95% CI 1.06–1.31) prevalence among respondents without current major depressive episode [23]. A nationally representative 2012 survey of 25,113 non-institutionalized Canadians age 15 years or older (Canadian Community Health Study—Mental Health) found a 5.4% (95% CI 0.9–5.0) prevalence of current CUD among respondents with current major depressive disorder, compared with a 1.1% (95% CI 0.9–1.3) prevalence among respondents without current major depressive disorder [24]. Conversely, the NESARC-III study found a 20.3% (SE 2.11%) prevalence of current major depressive disorder (aOR 1.3, 95% CI 0.94–1.79) and 9.2% (SE 1.70%) prevalence of persistent depression (aOR 1.9, 95% CI 1.09–3.30) among men with current CUD [20]. Among women with current CUD, the corresponding figures were 35.7% (SE 3.24%) prevalence of major depressive disorder (aOR 1.2, 95% CI 0.85–1.76) and 10.2% (SE 2.10%) prevalence of persistent depression (aOR 1.0, 95% CI 0.50–1.89). A secondary analysis of nationally representative survey data from 340,456 non-institutionalized US adults interviewed between 2005 and 2013 (NSDUH) found an 18.25% (SE 0.61) prevalence of past-year major depressive episode among the 10,795 respondents with past-year CUD [25]. The prevalence of major depressive episode was significantly lower among the 1,841 African-Americans with CUD (13.80%, 95% CI 11.39–16.63) and significantly higher among the 489 respondents who self-reported as "mixed race" (29.02%, 95% CI 19.80–40.38). The 2007 Australian NSMHW study found a 32.4% (SE 8.0%) prevalence of current major depressive disorder and 10.8% (SE 5.9%) prevalence of dysthymia among respondents with current CUD [4]. The ORs, compared with current cannabis users without current CUD, were 2.3 (95% CI 0.7–7.6) for major depressive disorder and 0.9 (95% CI 0.1–9.5) for dysthymia, suggesting that cannabis use, rather than CUD itself, is a significant risk factor for having depression. Also consistent with this interpretation is a meta-analysis including 14 published longitudinal studies of cannabis use and depression involving 76,058 participants [26]. The OR for heavy cannabis users (CUD or at least weekly use) subsequently developing depression (controlling for presence of depression at baseline) was 1.62 (95% CI 1.21–2.16) compared with light users (less than weekly) or nonusers. The OR for all users compared with nonusers was lower (1.17, 95% CI 1.05–1.30).

Similar patterns of comorbidity are found in large-scale studies of patients with a history of psychiatric treatment. The NSW hospital study found a 10.9% prevalence of major depressive disorder among patients hospitalized with CUD (OR 8.7, 95% CI 8.1–9.3) [6]. A Danish cohort study of 197,057 individuals treated for depression from 1969 to 2014 (derived from several national population-based registries) found a 2.1% prevalence of comorbid CUD [27]. A Norwegian cohort study of 87,540 patients born between 1950 and 1989 and treated for depression between 2009 and 2014 (derived from the Norwegian Patient Registry) found a 2.0% 5-year prevalence of CUD [28]. The Madrid mental health clinic study found a 19.5% prevalence of current major depressive episode among the 135 outpatients with current CUD and a 14.3% prevalence of current dysthymia [7].

Two community-based, prospective, longitudinal epidemiological studies shed light on the relationship between CUD and depression. A study that interviewed 1,920 non-institutionalized adults in the Baltimore, MD, metropolitan area in 1980 (Baltimore Epidemiologic Catchment Area [ECA] study) and re-interviewed them 14–16 years later found that, among those without depressive symptoms at baseline, presence of CUD at baseline made it significantly more likely to have depressive symptoms at follow-up than among respondents without baseline CUD (OR 4.00, 95% CI 1.23–12.97) [29]. Conversely, among respondents without CUD at baseline, presence of depressive symptoms at baseline was not associated with increased prevalence of CUD at follow-up, either with or without adjustment for age, sex, and presence of other SUDs. A study that interviewed 43,093 non-institutionalized US adults in 2001–2002 and re-interviewed 34,653 of them 3 years later (NESARC waves I and II) found that, among those without major depressive disorder at baseline, respondents with CUD at baseline were significantly more likely to have major depressive disorder at follow-up than were those without CUD or alcohol use disorder at baseline (OR 2.02, 95% CI 1.35–3.04) [30]. Conversely, among those without CUD at baseline, respondents with major depressive disorder at baseline were significantly more likely to have CUD at follow-up than those without baseline major depressive disorder (OR 5.23, 95% CI 1.28–21.34).

Treatment

Adults with comorbid depression and CUD may be more likely to seek treatment than those with only CUD, as would be expected from Berkson's bias. A secondary analysis of data from the 2005 to 2013 US NSDUH found that respondents with comorbidity were significantly more likely to have used cannabis-related treatment services in the past year than were respondents without a major depressive epi-

sode within the past year (aOR 1.74 [adjusted for sociodemographic characteristics and presence of other SUDs], 95% CI 1.29–2.34) [25].

There are relatively few published clinical trials of treatment for comorbid CUD and depression; many studies include cannabis users but do not provide a specific use disorder diagnosis [31–33]. A small controlled clinical trial in Australia randomly assigned 97 adults with comorbid major depressive disorder and "problematic" cannabis (71%) and/or alcohol (54%) use to either brief intervention (one motivational interview followed by no further treatment) or to 10 weekly sessions of combined motivational interviewing/cognitive behavioral therapy (CBT), delivered either in person or via computer [34]. Combined treatment was significantly more effective than brief intervention in reducing depressive symptoms and cannabis-related problems over the 12-month follow-up period, with computer-administered therapy showing the largest treatment effect.

Three controlled clinical trials of antidepressants (fluoxetine, venlafaxine) for the treatment of comorbid CUD and depression found mixed evidence of efficacy. A controlled clinical trial that randomized 70 adolescents/young adults (15–25 years old) with comorbid major depression and CUD to receive 12 weeks of manual-based motivation enhancement therapy (MET) and CBT plus either fluoxetine (20 mg daily) or placebo found no significant benefit from fluoxetine; both treatment groups showed comparable significant decreases in depressive symptoms, cannabis-related problems, and frequency of cannabis use [35], with comparable improvement in both groups persisting at 1-year follow-up [36]. The investigators attributed fluoxetine's lack of efficacy to the robust effect of CBT. An earlier clinical trial by the same research group that evaluated a subgroup of 22 adults with CUD and comorbid major depression and alcohol use disorder (from among 51 adults with comorbid major depression and alcohol use disorder) randomized to 12 weeks of weekly supportive psychotherapy plus fluoxetine (20–40 mg daily) or placebo found that fluoxetine significantly reduced depressive symptoms and the quantity and frequency of cannabis use [37]. A controlled clinical trial that randomly assigned 103 adults with comorbid CUD and major depressive disorder or dysthymia to 12 weeks of manual-based weekly CBT plus either venlafaxine-extended release (up to 375 mg daily) or placebo found venlafaxine associated with significantly lower likelihood of achieving abstinence (11.8% vs. 36.5%); both treatment groups had comparable significant improvement in depression [38].

Bipolar Disorder

Epidemiology

A systematic review and meta-analysis of 9 published community-based epidemiological surveys involving 218,397 respondents found a prevalence of around 20% for current CUD among respondents with bipolar disorder (including bipolar I disorder) and a prevalence of around 10% for bipolar disorder among respondents with current CUD [39]. A systematic review and meta-analysis by the same research group that included 78 published studies of clinical populations (both inpatient and outpatient) found similar rates of comorbidity, in both directions [40]. For example, the 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with current bipolar disorder to be 14.6% (SE 1.64) for bipolar I disorder (aOR 5.0, 95% CI 3.65–6.75) and 2.7% (1.10–6.62%) for bipolar II disorder (aOR 2.7, 95% CI 1.10–6.62) [19]. Conversely, the NESARC-III study found a 8.8% (SE 1.44%) prevalence of current bipolar I disorder (aOR 1.6, 95% CI 0.93–2.59) and 0.8% (SE 0.41%) prevalence of current bipolar II disorder (aOR 0.9, 95% CI 0.28–3.07) among men with current CUD [20]. Among women with current CUD, the corresponding figures were 9.0% (SE 1.69%) prevalence of current bipolar I disorder (aOR 1.3, 95% CI 0.75–2.18) and 1.5% (SE 0.89%) prevalence of current bipolar II disorder (aOR 1.3, 95% CI 0.32–5.40). The 2007 Australian NSMHW study found a 7.8% (SE 3.3%) prevalence of current bipolar disorder among respondents with current CUD [4]. The OR, compared with current cannabis users without current CUD, was 1.5 (95% CI 0.2–8.7), suggesting the CUD itself is not a significant risk factor for having bipolar disorder.

Similar patterns of comorbidity are found in large-scale studies of patients with a history of psychiatric treatment. The NSW hospital study found a 5.7% prevalence of bipolar disorder among inpatients with CUD (OR 17.6, 95% CI 16.0–19.4) [6]. A Danish cohort study of 24,567 individuals treated for bipolar disorder from 1969 to 2014 (derived from several national population-based registries) found a 3.3% prevalence of comorbid CUD [27]. A Norwegian cohort study of 15,540 patients born between 1950 and 1989 and treated for bipolar disorder between 2009 and 2014 (derived from the Norwegian Patient Registry) found a 3.3% 5-year prevalence of CUD [28]. The Madrid mental health clinic study found a 29.3% prevalence of current bipolar disorder among the 135 outpatients with current CUD [7].

Treatment

A recent review of treatment for bipolar disorder and comorbid SUD concluded that integrated psychosocial treatment incorporating elements of MET and CBT with components targeted to both disorders was more effective than generic 12-step enhancement or counseling, based on a limited number of small clinical trials [41]. However, the review did not identify any studies specifically focused on CUD.

A controlled clinical trial that randomly assigned 25 adolescents with a mood or anxiety disorder or ADHD (70% with bipolar disorder) and comorbid SUD (56% CUD + alcohol use disorder, 8% CUD only) to receive 6 weeks of weekly interpersonal therapy plus lithium (targeted to serum level of 0.9 meq/L) or placebo found that lithium significantly reduced mood symptoms and substance use (assessed with urine toxicology screens) [42].

Anxiety Disorders

A meta-analysis of 11 published epidemiological studies (cross-sectional or prospective cohort) involving non-institutionalized individuals found a significant association between anxiety disorders and CUD (OR 1.87, 95% CI 1.43–2.44 for those with vs. without CUD) [43]. The 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with a current anxiety disorder to be 5.4% (SE 0.46) (aOR 2.8, 95% CI 2.24–3.39) [19]. For specific anxiety disorders, the prevalence of current CUD was 6.9% (SE 1.35) (aOR 2.6, 95% CI 1.64–4.06) for agoraphobia, 7.1% (SE 0.85) (aOR 3.7, 95% CI 2.79–5.02) for generalized anxiety disorder, 8.3% (SE 1.05) (aOR 3.3, 95% CI 2.50–4.48) for panic disorder, 6.3% (SE 0.99) (aOR 2.3, 95% CI 1.61–3.27) for social anxiety disorder (social phobia), and 4.0% (SE 0.54) (aOR 1.7, 95% CI 1.28–2.29) for any specific phobia [19]. Conversely, the NESARC-III study found a 23.4% (SE 2.3) prevalence of any current anxiety disorder (aOR 1.2, 95% CI 0.88–1.56) among men with current CUD [20]. Among women with current CUD, the corresponding figure was 36.1% (SE 3.74) (aOR 0.8, 95% CI 0.58–1.23). Among men, the prevalence of specific anxiety disorders among those with current CUD was 1.6% (SE 0.50) (aOR 0.3, 95% CI 0.16–0.73) for agoraphobia, 12.2% (SE 1.88) (aOR 1.2, 95% CI 0.79–1.92) for generalized anxiety disorder, 7.4% (SE 1.20) (aOR 1.3, 95% CI 0.83–2.10) for panic disorder, and 7.3% (CI 0.66–1.55) for any specific phobia. The corresponding figures for women were 9.0% (SE 2.11) (aOR 1.3, 95% CI 0.67–2.79) for agoraphobia, 19.9% (SE 3.19) (aOR 1.3, 95% CI 0.83–2.19) for generalized anxiety disorder, 15.2% (SE 2.81) (aOR 0.9, 95% CI 0.50–1.57) for panic disorder, 7.2% (SE 1.76) (aOR 0.6, 95% CI 0.32–1.04) for social anxiety disorder, and 9.9% (SE 1.93) (aOR 0.5, 95% CI 0.32–0.87) for any specific phobia. These findings suggest a unidirectional pattern of comorbidity for anxiety disorders and CUD: CUD has a greater than chance association with anxiety disorder (reflected in ORs significantly greater than 1), while anxiety disorders don't have a significant association with CUD.

The 2007 Australian NSMHW study found a 40.5% (SE 7.7) prevalence of any current anxiety disorder among respondents with current CUD, compared with 20.8% (SE 2.1) among current cannabis users without CUD and 11.2% (SE 0.5) among current nonusers [4]. The OR for having any anxiety disorder was 1.1 (95% CI 0.6–2.2) for current cannabis users with CUD vs. current users without CUD and 0.7 (95% CI 0.5–0.9) for current nonusers vs. current users without CUD. For specific anxiety disorders, the prevalence among those with current CUD was 5.2% (SE 2.7) for agoraphobia (OR 2.2, 95% CI 0.4–12.8 vs. current users without CUD; OR 1.8, 95% CI 0.6–5.0 for nonusers vs. users), 19.0% (SE 6.7) for generalized anxiety disorder (OR 1.7, 95% CI 0.5–6.4 vs. current users without CUD; OR 1.3, 95% CI 0.6–2.5 for nonusers vs. users), 7.4% (SE 5.7) for panic disorder (OR 0.9, 95% CI 0.0–33.6 vs. current users without CUD; OR 0.8, 95% CI 0.3–1.8 for nonusers vs. users), and 14.0% (SE 3.8) for social phobia (OR 0.9, 95% CI 0.3–2.8 vs. current users with CUD; OR 0.8, 95% CI 0.5–1.3 for nonusers vs. users). These findings suggest that cannabis use, but not CUD itself, is a significant risk factor for anxiety disorder.

A prospective longitudinal study that followed almost 35,000 non-institutionalized US adults over 3 years starting in 2001–2002 (NESARC-I waves 1 and 2) found no significant associations between CUD and anxiety disorders, either with or without adjustment for sociodemographic characteristics and other psychiatric disorders [44]. Among respondents with CUD (but no anxiety disorder) at baseline (n = 319), there was no increased prevalence of any anxiety disorder at 3-year follow-up (aOR 0.99, 95% CI 0.65–1.5) nor of any specific anxiety disorder: generalized anxiety disorder (aOR 1.08, 95% CI 0.61–1.93), panic disorder (aOR 1.69, 95% CI 0.88–3.25), social anxiety disorder (aOR 1.75, 95% CI 0.95–3.23), or any specific phobia (aOR 0.71, 95% CI 0.43–1.15). Conversely, among respondents with any anxiety disorder (but no CUD) at baseline, there was no increased prevalence of CUD at 3-year follow-up (aOR 0.68, 95% CI 0.41–1.14). This was also true for each specific anxiety disorder.

Large-scale studies of patients with a history of psychiatric treatment do find substantial comorbidity between CUD and anxiety disorders. The US NIS study found that 12.54% (95% CI 12.00–13.11) of adults hospitalized between 2007 and 2011 with CUD as their only SUD diagnosis also had an anxiety disorder diagnosis, compared with 7.47% (95% CI 7.34–7.61) among patients without a CUD diagnosis [5]. The NSW hospital study found a 3.4% prevalence of anxiety disorder among inpatients with CUD (OR 4.8, 95% CI 4.3–5.5) [6]. A Danish cohort study of 40,552 individuals treated for anxiety disorder from 1969 to 2014 (derived from several national population-based registries) found a 2.9% prevalence of comorbid CUD [27]. The Madrid mental health clinic study found a 23.3% prevalence of current anxiety disorder among the 135 outpatients with current CUD, a 15.8% prevalence of current agoraphobia, and a 10.5% prevalence of current social phobia [7].

Treatment

We are not aware of any published controlled clinical trials of treatment for CUD with a comorbid anxiety disorder. An open-label case series involving 59 adults with comorbid social anxiety disorder and SUDs (38% CUD, 73% alcohol use disorder, 32% opiate use disorder, 29% cocaine use disorder) found that 10 weeks of weekly group CBT targeted at both anxiety and substance use produced significant reductions in social anxiety-related symptoms and negative affect [45]. Data on cannabis use were not reported.

Post-traumatic Stress Disorder (PTSD)

Epidemiology

Several nationally representative, community-based epidemiological surveys show comorbidity between CUD and PTSD. The 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with current PTSD to be 9.4% (SE 0.94) (aOR 4.3, 95% CI 3.15–4.67) [19]. Conversely, the NESARC-III study found a 12.3% (SE 1.66) prevalence of current PTSD (aOR 1.7, 95% CI 1.12–2.57) among men with current CUD [20]. Among women with current CUD, the corresponding figure was 26.9% (SE 3.37) (aOR 1.6, 95% CI 1.01–2.48). The 2007 Australian NSMHW study found a 9.4% (SE 3.8) prevalence of PTSD among respondents with current CUD, compared with 8.1% (SE 1.8) among current cannabis users without CUD and 4.1% (SE 0.3) among current nonusers [4]. The ORs for having PTSD were not significantly different from 1 for current cannabis users with CUD vs. current users without CUD (OR 0.5, 95% CI 0.1–2.2) or for current nonusers vs. current users without CUD (OR 0.7, 95% CI 0.4–1.3).

Large-scale studies of patients with a history of psychiatric treatment also find substantial comorbidity between CUD and PTSD. A Danish cohort study of 7,343 individuals treated for PTSD from 1969 to 2014 (derived from several national population-based registries) found a 3.0% prevalence of comorbid CUD [27]. The Madrid mental health clinic study found a 4.5% prevalence of current PTSD among the 135 outpatients with current CUD [7].

Treatment

A recent systematic review and meta-analysis including 14 studies (involving 1,506 participants) of psychosocial treatment for PTSD and comorbid SUD found that individual therapies combining trauma-focused and SUD-focused components overall produced significantly more reduction in PTSD symptoms than single-component therapies but did not significantly reduce substance use [46]. However, few of these studies included substantial numbers of cannabis users, and none explicitly included participants with CUD.

A controlled clinical trial randomly assigned 44 adult women prisoners with PTSD and comorbid alcohol use disorder, 75% of whom were also heavy cannabis users, to receive 6–8 weeks of psychoeducational groups and individual drug counseling (based on a 12-step model) with or without a CBT module based on safety-seeking before discharge from a minimum-security residential facility [47]. There were no significant group differences in PTSD symptoms or substance use at 3- and 6-month follow-up, but there was a significant positive association between number of CBT sessions and reduction in PTSD symptoms and drug use. A small open-label trial involving 37 adolescents with PTSD and current substance use (but not necessarily a SUD) (81% cannabis users) found that 12 weeks of manualized group CBT with both trauma- and substance use-focused components was associated with significant reductions from baseline to end of treatment in PTSD and depressive symptoms and proportion of days of cannabis use (decreasing from 16% to 9%) [48]. Another controlled clinical trial involving adults with comorbid PTSD and SUDs randomized to 6 weeks of twice weekly individual CBT sessions targeted to both PTSD and SUD or SUD alone recently completed enrollment [49].

We are not aware of any published studies of pharmacological treatment of comorbid CUD and PTSD.

Obsessive–Compulsive Disorder (OCD)

Epidemiology

The 2007 Australian NSMHW study found a 19.9% (SE 7.4) prevalence of OCD among respondents with current CUD, compared with 4.6% (SE 1.2) among current cannabis users without CUD and 2.4% (SE 0.2) among current nonusers [4]. The ORs for having OCD were not significantly different from 1 for current cannabis users with CUD vs. current users without CUD (OR 2.3, 95% CI 0.6–8.7) or for current nonusers vs. current users without CUD (OR 0.8, 95% CI 0.4–1.6). A Danish cohort study of 5,953 individuals treated for OCD from 1969 to 2014 (derived from several national population-based registries) found a 2.3% prevalence of comorbid CUD [27]. The Madrid mental health clinic study found an 8.3% prevalence of current OCD among the 135 outpatients with current CUD [7].

Treatment

We are not aware of any studies on the treatment of comorbid CUD and OCD.

Schizophrenia

Epidemiology

There are relatively few community-based epidemiological studies that provide data on CUD comorbidity with schizophrenia, in part because the lifetime prevalence of schizophrenia in the general population is estimated at only 5.5 (SD 4.5) per 1,000 [50]. A nationally representative 2001–2002 survey of 43,093 non-institutionalized US adults (NESARC-I) found that 7.9% (95% CI 3.2–12.6) of respondents with lifetime schizophrenia (based on self-report of receiving this diagnosis from a doctor) also had a lifetime diagnosis of CUD [22]. The aOR (adjusted for sociodemographic characteristics) for a CUD diagnosis among respondents with schizophrenia and cannabis use (compared to cannabis users without any psychiatric disorder) was 0.8 (95% CI 0.1–4.0), suggesting that the presence of comorbid schizophrenia does not significantly enhance the transition from cannabis use to CUD. A nationally representative 1997 survey of 6,722 community-dwelling Australian adults (18–50 years old) (1997 NSMHWB) found a 16.2% prevalence of current CUD among the 99 respondents with current schizophrenia or schizoaffective disorder, compared with a 3.3% prevalence among respondents without schizophrenia (OR 5.86, 95% CI 3.37–10.18) [51]. A 2002 survey of 8,484 Britons (16–74 years old) living in households found a 6.9% prevalence of current CUD among the 68 respondents with current psychosis, compared with a 2.5% prevalence among respondents without current psychosis (OR 2.92, 95% CI 1.05–8.13) [52].

A systematic review and meta-analysis that included 10 published studies of patients in treatment found a median prevalence of 16.0% (interquartile range 8.6–28.6) for current CUD among patients with schizophrenia, with higher prevalence among first-episode patients than chronic patients (28.6% vs. 22.0%) and among younger than older patients (38.5% vs. 16.0%) [16]. Several more recent national studies of patients in treatment also find substantial comorbidity between CUD and schizophrenia. The US NIS study found that 19.51% (95% CI 18.48–20.58) of 65,767 adults hospitalized between 2007 and 2011 with CUD as their only SUD diagnosis also had a diagnosis of schizophrenia, psychosis, or delusional disorder, compared with a 3.94% (95% CI 3.76–4.12) prevalence among inpatients without a CUD diagnosis [5]. The NSW hospital study found a 15.0% prevalence of schizophrenia among inpatients with CUD (OR 34.8, 95% CI 32.7–37.0) [6]. A Danish cohort study of 53,035 individuals treated for schizophrenia from 1969 to 2014 (derived from several national population-based registries) found a 13.2% prevalence of comorbid CUD [27]. A Norwegian cohort study of 9,002 patients born between 1950 and 1989 and treated for schizophrenia between 2009 and 2014 (derived from the Norwegian Patient Registry) found a 6.7% 5-year prevalence of CUD [28].

Two large-scale studies of patients in treatment compared comorbidity prevalence in those with CUD only, a stimulant use disorder only, and both disorders. An Australian study of 13,624 adults (18–50 years old) admitted to public hospitals in New South Wales between 2000 and 2011 with a diagnosis of schizophrenia and who had at least 2 years of treatment within the subsequent 5 years found a 17.8% prevalence of CUD and 11.2% prevalence of CUD + stimulant use disorder, compared with a 2.8% prevalence among patients with stimulant use disorder only [17]. Patients with comorbid CUD only were significantly more likely to be men (OR 2.2, 95% CI 2.0–2.5) and younger than age 46 years (e.g., OR 2.0, 95% CI 1.6–2.6 for those 36–40 years old). The Chilean national registry study of patients entering addiction treatment between 2007 and 2013 found a 5.2% (95% CI 4.1–6.6) prevalence of schizophrenia and related psychoses among patients with CUD only, compared with 2.3% (95% CI 2.1–2.6) among patients with CUD + cocaine use disorder and 1.1% (95% CI 0.9–1.4) prevalence among patients with cocaine use disorder only (aOR 4.32, 95% CI 3.03–6.18) [21]. Patients with comorbid CUD + cocaine use disorder also had a significantly greater prevalence of schizophrenia than patients with cocaine use disorder only (aOR 1.92, 95% CI 1.52–2.42) but significantly lower than patients with CUD only. These findings suggest that comorbid schizophrenia is more strongly associated with CUD than with stimulant use disorder, even though acute intoxication with both types of drugs is associated with psychosis.

Treatment

The larger literature on cannabis use by individuals with schizophrenia and related disorders suggests that psychosocial treatment may reduce cannabis use and positive symptoms of schizophrenia [53–56]. However, findings from the small number of controlled clinical trials of psychosocial treatment involving adults with comorbid CUD and schizophrenia and related disorders suggest little or no benefit from CBT and MET. A controlled clinical trial (CapOpus) in Denmark involving 103 adults with comorbid CUD and psychosis (51% schizophrenia, 31% schizotypal disorder) who were randomized to 6 months of treatment as usual (medication and CBT focused on psychosis) without or with weekly CBT/motivational interviewing focused on cannabis use found that psychosocial treatment did not significantly reduce the self-reported frequency of cannabis use at end of treatment or 4-month follow-up [57]. Over the subsequent 4-year period, participants who received the cannabis-focused psychosocial treatment had more psychiatric hospital admissions (incidence rate ratio 2.24, 95% CI 1.65–3.03)

and more psychiatric emergency room contacts (incidence rate ratio 3.47, 95% CI 2.64–4.57) than those who received only treatment as usual, based on the Danish Psychiatric Central Research Register [58].

A controlled clinical trial in Ireland involving 88 adults with comorbid cannabis dependence and early onset (within 3 years) psychosis (55% with schizophrenia, schizoaffective disorder, or schizophreniform psychosis) who were randomized to 12 weeks of treatment as usual (multidisciplinary team providing antipsychotic treatment) without or with weekly CBT and motivational interviewing focused on cannabis use found the psychosocial treatment associated with better subjective quality of life at 3-month and 1-year follow-up, but no difference in cannabis use or psychosis symptoms [59].

A controlled clinical trial in Australia involving 130 adults with comorbid current SUD (73% CUD, 67.3% alcohol, 42% amphetamine) and psychotic disorder (62% schizophrenia, 12.6% schizoaffective disorder) who were randomized to treatment as usual (self-help booklet about substance use) without or with 10 weeks of weekly motivational interviewing/CBT focused on substance use found that the psychosocial treatment significantly decreased self-reported frequency of cannabis use at 15 weeks, with no significant difference at 6 months or 12 months [60]. There was no difference in cannabis abstinence rates at any time point. The psychosocial treatment modestly reduced depressive symptoms and improved overall functioning, but had no effect on positive or negative symptoms of schizophrenia.

A controlled clinical trial in the United States involving 31 adults with comorbid schizophrenia and CUD (77%) and/or alcohol use disorder (77%) randomized to usual care or 18 months of cognitive enhancement therapy (individual, group, and computer-based sessions focused on goal setting, motivation for treatment, stress and emotion management, and improving social interactions, plus psychoeducation on substance use and schizophrenia) found that the psychosocial treatment significantly improved social adjustment and emotional function and significantly reduced frequency of self-reported alcohol use, but had no effect on cannabis use [61].

Findings from several small controlled clinical trials of antipsychotic medication treatment of comorbid CUD and schizophrenia suggest little or no benefit, with the possible exception of clozapine [53, 62]. A controlled clinical trial involving 31 adults with comorbid CUD and schizophrenia or schizoaffective disorder who were randomly assigned to 12 weeks of continuing their current antipsychotic medication or switching to clozapine (400–550 mg/day) found that clozapine significantly decreased cannabis use (by about 4.5 joints/week) but had no significant effect on schizophrenia symptoms or overall functioning [63]. A clinical trial involving 30 adults with comorbid CUD and schizophrenia, schizoaffective disorder, or schizophreniform disorder who were openly randomized to 12 months of clozapine (50–425 mg daily) or ziprasidone (80–400 mg daily) found that both treatment groups had comparable significant reductions in cannabis use, with clozapine producing greater reduction in positive symptoms of schizophrenia and more side effects (primarily hypersalivation) [64]. A controlled clinical trial involving 28 adults with comorbid SUD (93% CUD, 79% cocaine use disorder) and schizophrenia or schizoaffective disorder who were randomized to 10 weeks of risperidone (9 mg/day) or olanzapine (20 mg/day) found no significant change in cannabis use (proportion of THC-negative urine samples) in either treatment group [65].

Two open-label within-subject trials conducted by the same research group in Montreal, Canada, found some benefit in patients with comorbid schizophrenia-spectrum disorders switched from another antipsychotic medication (not clozapine) to 12 weeks of quetiapine (200–800 mg daily). The first trial, involving 24 adults with comorbid schizophrenia (58%), schizoaffective disorder (33%), or schizophreniform disorder (8%) and SUDs (63% CUD, 42% alcohol, 33% stimulants, 38% poly-substance use), found a significant decrease in self-reported cannabis use and craving, but no change in proportion of cannabis-positive urine tests [66]. The second trial, involving 26 adults with comorbid schizophrenia (58%), schizoaffective disorder (35%), or schizophreniform disorder (8%) and SUDs (58% CUD, 46% alcohol, 35% stimulants, 38% poly-substance use), found a significant decrease in self-reported substance use and severity of substance dependence (based on DSM-IV dependence criteria), as well as decreased positive and negative symptoms of schizophrenia [67]. These findings should be interpreted cautiously because of the weak study design and potential for quetiapine itself to be abused [68].

Attention-Deficit/Hyperactivity Disorder

Epidemiology

A 2004–2005 study of 33,488 non-institutionalized US adults (NESARC-I, wave 2) found about a 30% prevalence of lifetime CUD (varying by attention-deficit/hyperactivity disorder [ADHD] subtype: inattentive, hyperactive-impulsive, or combined) among the 965 respondents with ADHD, compared with 5% among the 15,614 respondents without ADHD or ADHD-type symptoms (aOR 2.14 [adjusted for socioeconomic characteristics, conduct disorder, major depression, and anxiety disorder], 95 CI 1.58–2.90) [69]. The 17,009 respondents with ADHD-type symptoms (but not meeting full DSM-IV diagnostic criteria for ADHD) also had significantly greater prevalence of lifetime CUD (10%; aOR 1.29, 95% CI 1.20–1.38). A 2010–

2011 study of 5,103 male Swiss Army conscripts found a 21.9% prevalence of current CUD among the 215 conscripts with current ADHD, compared with an 8.0% prevalence among conscripts without current ADHD (chi-square 48.43, P < 0.001) [70].

The US NIS study found a 2.82% (95% CI 2.64–3.01) prevalence of attention-deficit, conduct, or disruptive behavior disorder diagnosis among the 65,767 inpatients with CUD as their only SUD diagnosis, compared with a 0.63% (95% CI 0.61–0.65) prevalence among inpatients without any CUD diagnosis [5]. Conversely, a study of 1205 adults seeking treatment for SUD in 7 European countries (International ADHD in Substance Use Disorders Prevalence [IASP] Study) found a 22% prevalence of ADHD among the 129 respondents with CUD (OR 1.7, 95% CI 1.0–2.9) [71].

A meta-analysis of nine published prospective, longitudinal studies found that children with ADHD were significantly more likely to have CUD at follow-up (as adolescents/young adults) than those who did not have childhood ADHD (OR 1.58, 95% CI 1.16–2.14) [72]. However, a prospective longitudinal study of 1,512 11-year-old twins (Minnesota Twin Family Study) found no significant association between lifetime ADHD at study entry and CUD at age 18 years (aOR 0.58 [adjusted for conduct disorder], 95% CI 0.28–1.20) [73]. This finding suggests that some of the observed associations between CUD and ADHD may be confounded by comorbid conduct disorder.

Treatment

A controlled clinical trial that randomized 46 adults with comorbid cannabis dependence and ADHD (DSM-IV criteria) to 12 weeks of treatment with atomoxetine (80–100 mg daily) or placebo found that atomoxetine significantly reduced some ADHD symptoms, but had no significant effect on cannabis use [74].

Impulse Control Disorders

Epidemiology

We are aware of only two epidemiological studies that provide data on the comorbidity of CUD and impulse control disorders, both of which found a significant association between CUD and impulse control disorders (although without controlling for potential confounds). A reanalysis of data from a 2001–2002 nationally representative survey of 9,282 community-dwelling US adults (National Comorbidity Survey Replication [NCS-R]) found a current CUD prevalence of 7.2% among the 207 respondents with current intermittent explosive disorder (applying DSM-5 diagnostic criteria), compared with a prevalence of 0.6% among respondents without current intermittent explosive disorder (OR 6.65, 95% CI 3.58–12.35) [75]. The US NIS study found a 1.15% (95% CI 1.03–1.28) prevalence of any impulse control disorder diagnosis among the 65,767 inpatients with CUD as their only SUD diagnosis, compared with a 0.16% (95% CI 0.14–0.17) prevalence among inpatients without any CUD diagnosis [5].

Treatment

We are not aware of any published clinical trials of treatment for comorbid CUD and impulse control disorders.

Personality Disorders

Epidemiology

The 2012–2013 NESARC-III study in the United States found the prevalence of current CUD among those with a current personality disorder to be 8.6% (SE 0.46) (aOR 4.8, 95% CI 3.96–5.75) [19]. For specific personality disorders, the prevalence of current CUD was 11.2% (SE 0.75) (aOR 4.0, 95% CI 3.46–4.72) for schizotypal, 9.5% (SE 0.56) (aOR 4.5, 95% CI 3.96–5.19) for borderline, and 11.7% (SE 0.87) (aOR 4.7, 95% CI 4.07–5.34) for antisocial personality disorder (ASPD). Conversely, the NESARC-III study found a 48.2% (SE 2.51) prevalence of any current personality disorder (aOR 2.0, 95% CI 1.56–2.65) among men with current CUD [20]. Among women with current CUD, the corresponding figure was 58.6% (SE 3.17) (aOR 3.1, 95% CI 2.14–4.35). Among men, the prevalence of specific current personality disorders among those with current CUD was 24.9% (SE 2.17) (aOR 1.3, 95% CI 0.98–1.85) for schizotypal, 39.1% (SE 2.32) (aOR 2.0, 95% CI 1.46–2.67) for borderline, and 21.8% (SE 2.12) (aOR 1.5, 95% CI 1.08–2.02) for antisocial. The corresponding figures for women were 33.5% (SE 3.21) (aOR 2.0, 95% CI 1.26–3.18) for schizotypal, 49.9% (SE 3.21) (aOR 1.9, 95% CI 1.14–3.02) for borderline, and 16.1% (SE 1.95) (aOR 1.7, 95% CI 1.13–2.58) for antisocial.

The US NIS study found a 7.62% (95% CI 7.12–8.15) prevalence of any personality disorder diagnosis among the 65,767 hospitalized inpatients with CUD as their only SUD diagnosis, compared with a 1.41% (95% CI 1.33–1.48) prevalence among inpatients without a CUD diagnosis [5]. The NSW hospital study found a 9.2% prevalence of personality disorder among inpatients with CUD (OR 27.5, 95% CI 25.4–29.7) [6]. A Danish cohort study of 72,791 individuals treated for personality disorders from 1969 to 2014 (derived from several national population-based registries) found a

5.6% prevalence of comorbid CUD [27]. Among the 5,640 individuals with schizotypal disorder, 11.6% had comorbid CUD. These findings suggest a significant association between CUD and personality disorders among patients in treatment.

Treatment

A controlled clinical trial involving 136 young adults with cannabis dependence (DSM-IV criteria), 44% with comorbid antisocial personality disorder (ASPD), compared 8 weeks of manualized weekly MET/CBT with or without contingency management vs. weekly manualized individual drug counseling with or without contingency management [76]. MET/CBT was significantly more effective than drug counseling, with comparable effectiveness in the participants with ASPD (i.e., there was no significant ASPD x treatment interaction).

Adjustment Disorders

Epidemiology

We are aware of only one published study on the epidemiology of comorbid CUD and adjustment disorders. The US NIS study found a 2.88% (95% CI 2.66–3.12) prevalence of any adjustment disorder diagnosis among the 65,767 inpatients with CUD as their only SUD diagnosis, compared with 0.64% (95% CI 0.61–0.67) among inpatients without a CUD diagnosis [5], suggesting a significant association between CUD and adjustment disorders among patients in treatment.

Treatment

We are not aware of any published clinical trials on the treatment of comorbid CUD and adjustment disorder.

Conclusions

Adults with current CUD have a current prevalence of most major psychiatric disorders that is substantially greater than the prevalence of those disorders in the population without CUD, both in the community-living setting and in clinical settings. For example, prevalence rates for major psychiatric disorders in recent nationally representative epidemiological surveys in the United States and Australia range from 20 to 32% for depression, 8 to 9% for bipolar disorder, and 23 to 40% for anxiety disorders. Odds ratios for psychiatric comorbidity (compared with populations without CUD) are significantly greater than 1 in most studies, suggesting that the comorbidity is not due to chance. There is also substantial comorbidity in the reverse direction, i.e., prevalence of CUD in those with psychiatric disorders: 4–6% in depression, 15% in bipolar disorder, 5% in anxiety disorders, and 7–16% in schizophrenia. A similar pattern generally holds for comorbidity prevalence rates in clinical (treatment) populations.

Whether these statistical associations represent an actual causal relationship remains unclear. Few studies report the temporal order of onset of CUD and the psychiatric disorder; and few control for the numerous potential confounding factors, i.e., antecedent risk factors that may be common to both CUD and the psychiatric disorder, such as age, gender, socioeconomic status, history of abuse, substance use, and other psychiatric disorders. Genetic and twin studies might be informative, but these almost exclusively focus on cannabis use among those with psychiatric disorders, rather than CUD and psychiatric comorbidity.

Despite the substantial prevalence of CUD and psychiatric comorbidity and its clinical relevance for prognosis and treatment, there are relatively few clinical trials evaluating treatment. Thus, it is not surprising that no medication is approved for such an indication by the US Food and Drug Administration (FDA) or any other national regulatory authority. Single, small-scale controlled clinical trials suggest that lithium may be effective for adolescents with bipolar disorder [42] and clozapine for adults with schizophrenia [63]. There is a similar scarcity of high-quality evidence for psychosocial treatments [77]. Several small-scale, controlled clinical trials suggest that combined MET/CBT with components focused on both CUD and the psychiatric disorder can be effective in reducing cannabis use and improving psychiatric symptoms.

Current gaps in the evidence base regarding CUD and psychiatric comorbidity suggest several areas that warrant further research. These include large-scale, representative epidemiological surveys that explicitly diagnose CUD and the psychiatric comorbidity, evaluate relevant potential confounds (e.g., cannabis and other substance use), and use these data to calculate odds ratios in relation to relevant comparison populations; large-scale, long-term prospective longitudinal studies that carefully evaluate participants at baseline to exclude those with one comorbid disorder so that the incidence over time of the other disorder can be accurately assessed; and genetic and twin studies that focus on diagnosed disorders in addition to substance use. There is also an urgent need for high-quality controlled clinical trials of both pharmacological and psychosocial treatments (and their combination) that involve participants with specifically diagnosed CUD and comorbid psychiatric disorders. Promising medications to study include lithium for comorbid bipolar disorder and clozapine (and possibly quetiapine) for comorbid schizophrenia.

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The Association Between Cannabinoids and Psychosis

14

Sai Krishna Tikka and Deepak Cyril D'Souza

Introduction

The association between cannabinoids and psychosis was recognized centuries ago. Chinese emperor Sheu Nang is reported to have described cannabis as a "psychic liberator" as early as 2737 BC [1]. Interestingly, it is believed that the "hemp" plant developed its "narcotic" property after it reached India, from Central Asia and Europe. Previously in Central Asia and Europe, it was known only as a fiber-yielding species – hemp. From India, this plant with its newly acquired property traveled through the Himalayan valleys, Tibet, and China back to Central Asian countries of Persia, Syria, Arabia, and Egypt and also eastward to Malaya [2]. Persia, Syria, is where the "Old Man of the Mountain" (Hassan-i Sabbah) used "hashish" to drug his factions, led them to "paradise" (good trip), and then made them his disciples. Hassan-i Sabbah and his disciples formed the sect "Nizari Ismailis" (called "Haschichins" or "Assassins") which posed a military threat to the authority through a series of assassinations of key figures [3, 4].

Although, medical literature referring to medicinal benefits of cannabis date back to times as early as 1400–2000 BC [5], reportedly, Iban Beitar was the first physician to point out the mental symptoms with use of cannabis (hemp)[2]. Later in 1845 French psychiatrist Jacques-Joseph Moreau described psychotic symptoms with hashish use [6]. He described that hashish induced similar manifestations – hallucinations, paranoia, and thought disorders – as in other psychotic patients [7].

There prevalence of the use of cannabis has increased over time. Recent data suggests that an estimated 3–5% of the world population has at least one fairly recent cannabis use [8]. A very recent epidemiological study conducted in the USA reports that 1 in 16 community residents in the 12- to 24-year age range starts to use cannabis each year [9]. The National Survey on Drug Use and Health reported a significant decline in the "risk perception" of smoking marijuana in adolescents [10]. Some reports suggest that increase in the use of cannabis is contingent upon the younger generation's choice to avoid "hard drugs" and a perception that cannabis is a "soft/benign drug" [11]. Furthermore, there is a recent trend in the recreational use of an array of substances, henceforth referred to as "Spice" or K2, containing highly potent synthetic cannabinoids. Over the course of this chapter, we review a large evidence pool that suggests associations between cannabinoid exposure and psychosis outcomes that constitute the exogenous hypothesis.

Cannabinoids: Constituents and Potency

Phytocannabinoids

The cannabis plant has more than 540 natural compounds including about 100 cannabinoids (aryl-substituted meroterpenes) [12, 13]. Among the cannabinoids, delta-9-tetrahydrocannabinol (Δ9-THC) is the principal psychoactive constituent of cannabis. The principal active metabolite of Δ9-THC, 11-hydroxy-THC (11-OH-THC), is more potent than Δ9-THC, and the time course of 11-OH-THC levels in blood correlates well with the psychological effects of inhaled and oral Δ9-THC [14]. The principal inactive metabolite is 11-nor-9-carboxy-THC or THC-COOH, and it is what is tested for in blood or urine. Herbal cannabis contains tetrahydrocannabinolic acid (THCA), which is converted

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into Δ9-THC after heating. Cannabidiol (CBD) is another important cannabinoid present in cannabis. While it does not have any psychoactive effects, it may modulate the effects of THC. Behavioral and neurochemical studies, both in humans and animals, suggest that CBD may have antianxiolytic and antipsychotic effects and may block the conversion of Δ9-THC to 11-OH-THC [15–17]. Iseger and Bossong (2015)[18] reported that (a) CBD counteracts psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration; (b) CBD may lower the risk for developing psychosis from cannabis use; (c) CBD and THC have opposite effects on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus, and prefrontal cortex; and (d) CBD may be an effective, safe, and well-tolerated antipsychotic compound useful in the treatment of patients with psychotic symptoms. As both Δ9-THC and CBD are the main constituents of herbal cannabis plant, the net effect of cannabis is related to the relative proportion of Δ9-THC and CBD, i.e., THC/CBD ratio. This ratio varies significantly across various cannabis samples. Although the THC/CBD ratio offers the net psychotropic effect, levels of Δ9-THC have been used to quantify "potency" of cannabis. Besides, it has been experimentally documented that people titrate the amount they roll in joints according to concentrations of Δ9-THC and not CBD [19].

The potency of cannabis seems to have increased over the last few decades. In the USA, between 1980 and 1997, the Δ9-THC concentration of cannabis samples rose from less than 1.5% in 1980 to 4.2% in 1997 [20]. ElSohly et al. (2016) [21] find that the concentration of Δ9-THC in seized illicit cannabis plant materials in the USA has risen from about 4% in 1995 to 12% in 2014. Conversely, in the CBD content of cannabis has fallen from about 0.28% in 2001 to <0.15% in 2014. Thus, the THC/CBD ratio has increased from about 14 in 1995 to about 80 in 2014. These trends are not restricted to the USA but have also been observed in other countries too [22]. In addition to herbal cannabis, there are a range of products available on the market with very high concentrations of THC. For example, some products, e.g., wax and butane hash oil (BHO) that are made from extracting THC from cannabis using butane, contain up to 90% THC [23]. Moreover, these "cannabis concentrates," inhaled by a new method called "dabbing," have been shown to have considerable residual solvent and pesticide contamination [24]. In addition to inhaling, the traditional method of recreational use, a wide range of "edibles" in the form of cookies, brownies, lollipops, butter, etc., have become available. These orally consumed products have a different pharmacokinetic profile. Whereas the effects of inhaled THC or cannabis are felt almost immediately and can be titrated; with oral consumption, effects only emerge 60–90 minutes later and therefore cannot be titrated. Furthermore, there is a much greater degree of pharmacokinetic variability with oral consumption, and the duration of effects with oral consumptions is longer than inhaled use.

Synthetic Cannabinoids

Synthetic cannabinoids, also referred inaccurately to as "fake weed or synthetic marijuana," are among the most commonly encountered substances among the "designer drugs" or "new psychoactive substances" [25, 26]. In the USA, Spice users typically tend to be young, male, nonwhite and belong to groups who are trying to evade detection (prisoners, armed forces service personnel, etc.) [27, 28]. These synthetic cannabinoids are marketed under various trade names including "Spice," "K2," "Magic Gold," etc. [29]. These drugs are sprayed on an herbal substrate and mostly sold under the guise of "herbal incense" or potpourri. These drugs got the name "legal highs" as standard drug tests couldn't detect their use and because there were no laws prohibiting their use [30]. As regulatory bodies started banning these drugs once they were identified, other analogous synthetic cannabinoids that had not yet been banned began to become available [31]. While most of the earlier marketed illicit synthetic cannabinoids were derived from JWH-018 (class naphthoylindoles), the newer additions are either tetramethylcyclopropyl ketone- or indazole-derived cannabinoid derivatives (AB-PINACA, AB-CHMINACA) [32]. Recently, a ban on these compounds is also being imposed [31]. Nonetheless, detection of these newer compounds remains a challenge since the tests to detect these compounds lag behind their introduction and the addition of other compounds, e.g., vitamin E, interferes with identification [25].

Synthetic cannabinoids are in general more potent than THC by 10–200 times. Synthetic cannabinoids are full agonists at cannabinoid subtype 1 receptor (CB1R), while THC is a weak, CB1R partial agonist. Synthetic cannabinoids have greater affinity at CB1R than THC, which has a modest affinity [25]. Synthetic cannabinoids have been associated with robust and sometimes catastrophic effects including physical (seizures, cardiac defects, renal failure, as well as death) and psychological (psychotic symptoms, panic attacks, etc.) effects in addition to dependence-withdrawal and tolerance (for review see [25, 29, 33–36]). Furthermore, products containing synthetic cannabinoids typically do not contain CBD which has been reported to attenuate the anxiolytic and propsychotic effects of THC [37, 38]. Pertinently, a recent report suggests that psychotic symptoms were significantly greater in subjects using synthetic cannabinoids alone compared to those using phytocannabinoids either alone or in combination with synthetic cannabinoids [39].

The Brain Endocannabinoid (eCB) System

Since cannabinoids produce most of their behavioral effects via the brain endocannabinoid system, a brief review of the endocannabinoid (eCB) system is provided (for a more detailed review, see chapter xx). The eCB system is one of the most widespread systems in the central nervous system [40]. It consists of receptors, endogenous transmitters or endocannabinoids (eCB) and enzymes that synthesize and degrade eCBs. The two main receptors are the G-protein-coupled receptors - cannabinoid-1 receptor (CB1R) and cannabinoid-2 receptor (CB2R), but in addition, some cannabinoids also engage transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors (PPARs) [41–43] (see Table 14.1). The two most well-studied eCBs include the lipid ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The enzymes involved in the biosynthesis and degradation of AEA are N-acyl phosphatidylethanolamine-selective phospholipase D (NAPE-PLD) and fatty acid amide hydrolase [FAAH], respectively, while the enzymes involved in the biosynthesis and degradation of 2-AG are diacylglycerol lipase [DAG-L] and degradation monoacylglycerol lipase [MAG-L] and 2-arachidonoylglycerol hydrolase [ABHD6].

In contrast to other classical neurotransmitters, e.g., dopamine, that are synthesized ahead of time and stored in vesicles for release, AEA and 2-AG are synthesized on demand from their precursors present in lipid membranes, prompted by activation of G-protein-coupled receptors or by depolarization. After synthesis, eCBs are rapidly released into the extracellular space where they bind to and activate presynaptic or postsynaptic CB1R or CB2Rs, inhibiting the further release of neurotransmitters [40]. CB1Rs, densely expressed in the brain, are critical in mediating the psychoactive effects of cannabis, as they are the targets of THC, a partial agonist at this receptor. CB2Rs, in contrast, are mostly expressed peripherally (in the immune, gastrointestinal, and peripheral nervous systems).

While THC and the eCBs anandamide or 2-AG both activate CB1Rs in contrast to eCBs, exogenous cannabinoids, such as THC, are metabolized over several hours before being excreted. Thus, the duration of effects of THC and eCBs are rather different, with eCBs having brief effects and THC having prolonged effects. Thus, the effects of eCBs do not completely extrapolate to those of exocannabinoids and vice versa. The important role of the eCB in neurodevelopmental processes could explain why as discussed later adolescence is an important period of vulnerability to the effects the exogenous cannabinoids, potentially resulting in the disruption of eCB-mediated developmental processes.

Relationship between Cannabis and Psychosis: Clinical Presentation

There have been many attempts to characterize psychosis associated with cannabis. Almost 100 years ago, Dhunjibhoy described the "Indian Hemp Insanity" [2] as a toxic psychosis associated with the consumption of cannabis: "…….In larger doses there occur excitement, delusions, hallucinations, activity with a tendency to violence, ecstacy and deep sleep followed by forgetfulness of all but the initial symptoms." He suggested that hemp insanity presented either as acute mania, chronic mania, or dementia (dementia praecox). Characteristic symptoms of mania included auditory or visual hallucinations. While acute mania resolved with stoppage of drug,

Table 14.1 Components of the brain endocannabinoid system

Endogenous ligands (endocannabinoids)	Receptors (G- protein-coupled)	Enzymes*			
		AEA		2-AG	
		Synthesis	Cleavage/hydrolysis	Synthesis	Cleavage
N-arachidonoyl-ethanol-amine (AEA) (anandamide)	Type 1 cannabinoid receptor (CB1R)	*TRPV1 (Transient receptor potential vanilloid-1) is activated by both AEA and 2-AG			
		N-acyltransferase (NAT)	FAAH (Fatty acid amide hydrolase)	Phospholipase C-β (PLC-β)	MAGL (Monoacylglycerol lipase)
2-arachidonoyl-sn-glycerol (2-AG)	Type 2 cannabinoid receptor (CB2R)	NAPE-PLD (N-acyl phosphatidyl-ethanolamine-specific phospholipase D)	N-acylethanolamine-hydrolyzing acid amidase (NAAA)	DAGL (Diacylglycerol lipase)	α/β-hydrolase 6 and 12 (ABDH 6; ABDH 12)
	Type 3 cannabinoid receptor (CB3R, i.e. G protein-coupled receptor 55)	α/β-hydrolase 4 (ABDH 4)	Cyclooxygenase 2 (COX2)	Phospholipase A1 (PLA1)	Cyclooxygenase 2 (COX2)
		Phosphodiesterase	Lipoxygenase 12 and 15	Lyso-phospholipase C (lyso-PLC)	Lipoxygenase 12 and 15
		Phospholipase A2 (PLA2)	Cytochrome p450		Cytochrome p450
		Lyso-phospholipase D (lyso-PLD)			

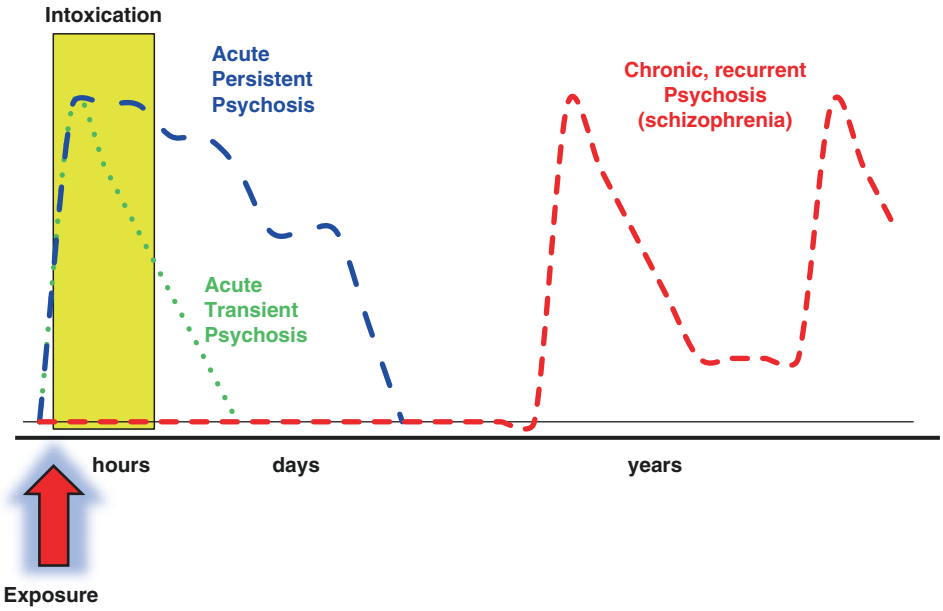

Fig. 14.1 Temporal relationships between exposure to cannabinoids and psychosis

Table 14.2 Relationships between cannabinoids and psychosis

	Onset of Psychosis in relation to Exposure		Duration of Psychosis			Resolution of Psychosis	
	Immediate	Delayed	Hours	Days	Weeks	Spontaneous Recovery	Requires intervention
1	+		+			+	
2	+			+			+
3		+		+	+		+

chronic mania persisted. Juan Carlos Negrete in 1973 [44] suggested that psychoses related to cannabis could be characterized according to the duration of psychosis, alteration of sensorium, the dose of cannabis, and the presence of affective symptoms:

1. Severe intoxication – cannabinoids taken in strong dose, psychotic symptoms with toxic (impaired sensorium) symptoms, limited to period of intoxication
2. Pathological intoxication – cannabinoids taken in average to moderate dose, affective > psychotic symptoms without toxic (impaired sensorium) symptoms, limited to period of intoxication
3. Acute cannabis psychoses – precipitated during cannabis intoxication but not limited to period of intoxication, may last as long as 15 days
4. Subacute and chronic cannabis psychoses – heavy, chronic use

He also described residual conditions including an amotivational syndrome.

With difficulty in dissecting "severe intoxication" from "pathological intoxication," and with "amotivational syndrome" being understood under "negative symptom" dimension of psychoses [45], D'Souza recently proposed a simpler classification [46] based on the temporal relationship between exposure and psychosis, the clinical significance of the psychosis, and the duration and recurrence of psychosis (see Fig. 14.1, Table 14.2):

1. Acute and transient psychosis (ATP) – time locked to exposure, lasting no more than the duration of intoxication (minutes to hours), and generally not requiring clinical intervention
2. Acute, immediate, persistent psychosis (AIPP) – time-locked to exposure, lasting days to weeks, i.e., beyond the duration of intoxication, and typically requiring clinical intervention
3. Chronic, delayed, persistent psychosis (CDPP) – occurring months to years later, i.e., not time locked to exposure, recurring, and requiring clinical intervention

The evidence for these relationships between cannabinoids and psychosis is presented below.

Acute and Transient Psychosis

Anecdotal Reports

There are several anecdotal reports describing psychotic symptoms that occur immediately following exposure to

phytocannabinoids, usually in moderate to large doses, that last only the period of intoxication and are self-remitting [2, 6, 15, 47–55]. The symptoms include depersonalization, derealization, paranoia, ideas of reference, flight of ideas, pressured thought, disorganized thinking, persecutory delusions, grandiose delusions, auditory and visual hallucinations, and impairments in attention and memory in an otherwise clear consciousness.

There are similar reports associated with the use of medicinal, synthetic cannabinoids such as dronabinol, its analog levonantradol and nabilone that have been used for their antiemetic and analgesic properties. The symptoms reported are "loss of control," thought disturbances, feelings of unreality, apprehension, fear and paranoia, anxiety and panic, dissociation, depersonalization, dysphoria, difficulty concentrating, hallucinations, other perceptual alterations, amnesia, and accompanying anxiety [56–70]. These effects have been reported to be related to both dose and duration of dosing. Levonantradol was later discovered to be a potent CB1R agonist and was abandoned because of a high incidence of intolerable behavioral side effects that included psychotic symptoms. However, a recent systematic review [71] concluded that there is no sufficient evidence to suggest that adults receiving cannabinoids for cancer chemotherapy-induced nausea and vomiting report hallucinations and paranoia. However, they report significantly greater "feeling high" and "euphoria" with their use.

There are several reports of psychosis with the recreational use of synthetic cannabinoids such as JWH-018 (class naphthoylindoles), tetramethylcyclopropyl ketone-, or indazole-derived cannabinoid derivatives (AB-PINACA, AB-CHMINACA) [25, 29, 33–35, 37–39, 72–90]. The psychotic symptoms reported include perceptual alterations, illusions, auditory and visual hallucinations, paranoia, agitation, aggression, catatonia, depersonalization, and dissociation.

Epidemiological Studies

Longitudinal epidemiological studies have shown a significant association between cannabinoid use and psychotic symptoms [91–96]. These studies report to have a dose-related response and to be greater in those predisposed for psychosis. By and large self-reports from population-based surveys state that 20–50% of individuals report paranoia, persecutory ideas, and hallucinations while under the influence of cannabis [97, 98].

Experimental Studies

Human laboratory studies (HLS) provide some of the most compelling evidence supporting the association between cannabinoids and psychosis. Broadly, HLS have been conducted on either healthy (without present/past/family history of psychosis) or patient/vulnerable participants (with present/past/family history of psychosis).

Healthy Individuals

One of the earliest experimental studies was conducted under the auspices of the LaGuardia Committee on Marihuana in 1944 [99]. This study reported that 12.5% of subjects experienced psychotic reactions at doses of about 30–50 mg oral and 8–30 mg smoked cannabis. In this study, the participants were prisoners, and a "healthy" status of them cannot be ascertained. Ames [100], in 1958, administered un-assayed oral doses of cannabis extract (~50 to 70 mg Δ9-THC) to 12 presumably healthy physicians elicited a range of psychotic symptoms including fragmented thinking, dissociation between thoughts and action, disturbed temporal and spatial perception, persecutory delusions, delusions of the presence of hidden recorders, fears of being hypnotized, subjected to ECT, or presciently developing schizophrenia, visual illusions and hallucinations, derealization and depersonalization, mood alterations, hypomania, anxiety, and memory deficits. Only one participant required intervention to control symptoms. Other quasi-experimental studies of cannabis (marijuana or/and its resins) have reported a range of dose-related psychotic symptoms (euphoria to striking hallucinations) with cannabis [101–105].

In the last decade and a half, there have been a number of tightly controlled laboratory studies reporting acute transient psychosis following the administration of cannabinoids in healthy individuals screened for current or past any psychiatric disorder (For review see Sherif et al. (2016) [17]). Psychotic symptoms in these studies were characterized on standardized rating scales such as the Positive and Negative Syndrome Scale (PANSS), Clinician Administered Dissociative States Scale (CADSS), Community Assessment of Psychic Experiences (CAPE), Psychotomimetic States Inventory (PSI), and Brief Psychiatric Rating Scale (BPRS). Various cannabinoids such as marijuana, Δ9-THC, nabilone, and dronabinol have been tested.

Schizophrenia is characterized by psychotic (positive) symptoms, negative symptoms, and cognitive deficits (Fig. 14.2). *Positive symptoms* that have been reported uniformly across these studies are suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, depersonalization, derealization, distorted sensory perceptions, altered body perception, feelings of unreality, and extreme slowing of time [68, 106–117]. Blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced rapport are the negative symptoms found [106, 118]. Importantly salience processing, proposed as a potential mechanism for schizophrenia psychopathology [119], has been found to be impaired following acute THC administration. Some studies have also demonstrated that cannabinoids can produce transient effects that resemble the *negative symptoms* of schizophrenia including blunted affect and emotional withdrawal.

Cannabis and other synthetic cannabinoids have been found to produce acute, transient, dose-related impairments

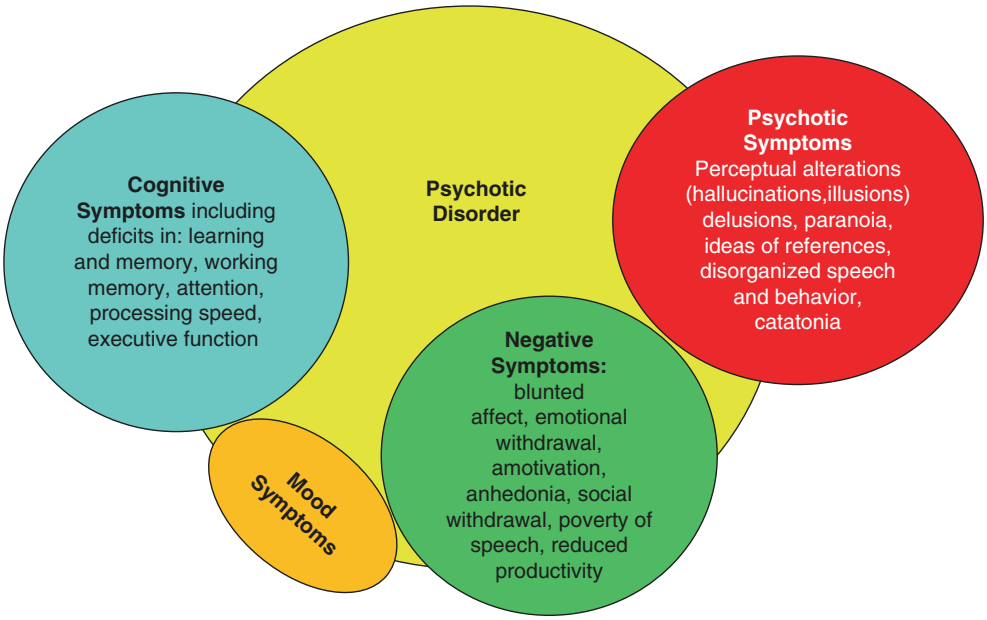

Fig. 14.2 Symptom domains of schizophrenia

in *cognitive deficits* that are also observed in psychotic disorders such as schizophrenia. Cannabis and cannabinoids produce an array of acute, transient, and dose-related impairments in sustained attention, divided attention, selective attention, signal detection and allocation of attention (P300), sensory gating (P50), working memory, spatial working memory and maze accuracy, verbal learning and recall, procedural memory, associative learning, time estimation, distance estimation, impulsivity, reaction time, information processing speed, tracking accuracy, and set shifting and psychomotor coordination [106, 107, 110, 111, 120–160]. Most of these effects peak about 15–45 minutes following exposure and subside thereafter. The most robust, acute, and incontrovertible cognitive effects of cannabinoids are on learning and memory [120, 121]. Cannabis and cannabinoids transiently impair immediate and delayed free recall of information presented after, but not before, drug administration in a dose- and delay-dependent manner. In particular, there is an increase in intrusion errors. Pfefferbaum suggested that the increase in intrusion errors may be the mechanism involved in some of the thought disorder observed with cannabis intoxication. Cannabinoids have also been shown to produce acute, transient *electrophysiological deficits* that are also associated with schizophrenia. Deficits in electrophysiological measures of information processing, such as neural oscillations and event-related potentials (ERPs) including the P300, have been reported in schizophrenia.

Deficits in P300 amplitude and latency have been demonstrated in patients with schizophrenia [161–169]. The P300 is related to directed attention, contextual updating of working memory, and the attribution of salience to deviant or novel stimuli. Several groups have demonstrated that cannabinoids decrease P300 amplitude but not latency in healthy individuals [111, 170, 171] suggesting that cannabinoids acutely disrupt cortical processes responsible for context updating and the automatic orientation of attention.

Neural oscillations in the gamma (ɣ)-band (30–80 Hz) play a key role in sensory registration and integration, associative learning, conscious awareness [172], and in the organization of brain networks [173]. Schizophrenia patients show evidence of abnormal neural oscillations and synchrony (reviewed in[174]). THC has been shown to disrupt γ-band neural oscillations in humans and that the disruption of γ-band neural oscillations was related to the THC-induced psychosis [175]. Theta Θ-band (4–8 Hz) oscillations are disrupted by cannabinoids in rats. In humans, cannabinoids have been shown to acutely disrupt theta band power [176, 177] consistent with studies in animals [178]. Furthermore, THC-induced theta deficits have been shown to correlate with memory performance [176]. Acute administration of THC in experimental conditions has been found to decrease theta oscillatory activity, in terms of resting state power, which correlated with working memory deficits or phase-locking factor evoked by working memory tasks [170, 176, 177, 179, 180].

Neural noise or task-irrelevant *random* neural activity has been shown to be increased in psychotic disorders [181–186]. Alteration in synchronized neural oscillations has been suggested as one of the mechanisms whereby cannabinoids induce psychosis [187]. THC at doses that produced psychosis-like effects increased neural noise in a dose-dependent manner [188]. Furthermore, THC-induced increases in neural noise were related to increases in THC-induced positive symptoms but not negative symptoms

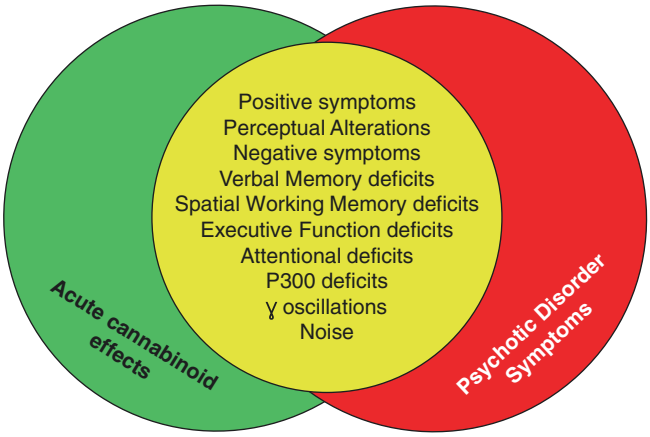

Fig. 14.3 Overlap between some of the acute effects of cannabinoids and some of the symptoms of schizophrenia

suggesting that increases in neural noise may contribute to the psychotomimetic effects of THC.

In summary, cannabinoids can produce an array of transient subjective, behavioral, cognitive, and psychophysiological effects known to be associated with schizophrenia (Fig. 14.3).

Psychiatric Patients

In 1934, Lindeman and Malamud administered unassayed doses of hashish to a group of schizophrenia patients and reported an exacerbation of their symptoms [189]. In 1948, Pond studied the psychological effects of synhexyl or parahexyl (n-hexyl-Δ^3THC), a synthetic homologue of THC, in depressive patients and reported depersonalization, somatic sensations, auditory/visual hallucinations, and schizophreniform thoughts in them [190]. Pond did not find improvement in depressive symptoms following synhexyl ingestion. There were few experimental studies of cannabinoid effects in psychiatric patients till the turn of the century.

D'Souza et al. reported for the first time the dose-related effects of THC in schizophrenia patients from a double-blind, randomized, placebo-controlled, crossover study. THC worsened positive symptoms, perceptual alterations, negative symptoms, and cognitive deficits. Furthermore, more schizophrenia patients had THC-induced clinically significant increases in psychosis relative to controls despite being clinically stable and receiving treatment with antipsychotic medications [130]. Schizophrenia patients were also more vulnerable to the memory impairing effects of THC. There were no "beneficial" effects of THC in the study. The investigators concluded that the lack of any observed beneficial effects of THC challenged the cannabis self-medication hypothesis in schizophrenia [130].

In another double-blind, placebo-controlled, crossover study, Henquet et al. [94, 191] reported that Δ9-THC acutely impaired memory and attention in both psychotic patients and controls. However, patients seemed to be less sensitive to the verbal memory effects of Δ9-THC than healthy controls, and the acute effects of Δ9-THC on attention were more pronounced in patients than in controls. In addition, the Val158Val genotype was shown to predict increased sensitivity to the acute effects of Δ9-THC on cognition and that it moderated the acute effects of Δ9-THC on psychotic symptoms. Such findings suggest that such higher-order gene level interactions may better explain individual differences in sensitivity to the acute effects of Δ9-THC on cognition and psychosis.

Schwarcz et al. (2009) [192] reported a case series of six treatment-resistant cannabis-dependent schizophrenia patients who received open-label dronabinol. Clinical improvement in conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, and overall functioning was observed. These findings suggest that there may be a subset of schizophrenia patients for whom THC does not worsen symptomatology and may even improve symptoms. Further controlled studies will be necessary to replicate these findings.

Whitfield-Gabrieli et al. (2017) [193] reported that the administration of oral or smoked THC reduced Default Mode Network (DMN) hyperconnectivity in patients with schizophrenia with comorbid cannabis use disorder. Interestingly, THC administration did not elicit significant changes in psychotic symptom severity. Most recently, as discussed later, Vadhan et al. (2017) reported that smoked THC worsened symptoms in clinical high risk for psychosis individuals.

Acute, Immediate, Persistent Psychosis (AIPP)

Clinical Presentation

AIPP occurs immediately following cannabinoid exposure and persists beyond the period of acute intoxication, lasting typically for days but sometimes up to weeks. While one of the earliest reports was of a series of a case series from India [48, 194], it appears to be a global phenomenon, with reports from various other countries [52, 195–202]. AIPP follows the consumption of large doses of cannabis and is characterized by hallucinations, paranoia, delusions, depersonalization, emotional liability, amnesia, confusion, and disorientation. The syndrome generally requires clinical intervention. After the cessation of cannabis use, the psychotic symptoms resolve within days to weeks, which is quicker in comparison with "endogenous" psychoses. Furthermore, psychosis tends not to relapse unless cannabis use resumes [203]; however, it is not clear how strong this finding is.

More recently, the recreational use of products containing synthetic cannabinoids, e.g., Spice and K2, in the USA, Europe, and other countries has been associated with psychosis that may persist beyond the period of acute intoxication, i.e., for days to weeks [25, 29, 33–35, 37–39, 72–88]. A whole range of psychotic symptoms have been reported including perceptual alterations, illusions, auditory and visual hallucinations, paranoia, agitation, aggression, catatonia, depersonalization, and dissociation. Interestingly, the alterations in motor behavior and presentation of extreme disorganization have bene described as "zombie-like behavior." In some instances, individuals in this state engaged in behavior that has resulted in significant self-harm [204]. Some of these cases have occurred following just one exposure while others have occurred in the context of repeated exposure. These presentations have occured both in individuals with and without a previous or family history of psychosis. The sudden onset of psychosis and degree of agitation typically warrants clinical intervention. Limited data suggest that managing acute psychosis and agitation with typical pharmacological interventions is challenging. Psychotic symptoms persist longer after cessation of use and in fact longer that its effects of motor depression and anxiety. Moreover, they may require medical intervention in the form of hospitalization [83].

There have also been reports of cannabinoid-related AIPP with use of high-potency phytocannabinoid preparations such as butane hash oil (marijuana wax) and wax dabs [205, 206]. The symptoms reported include incoherent speech, odd behaviors, dream-like state with perseverating thoughts, disorganization, thought blocking, and paranoia. The symptoms have been reported to last 2–3 weeks and require clinical intervention including treatment with antipsychotic medications.

Long-Term Course and Outcome

While case reports suggest that when cannabinoid use is stopped, the acute psychotic episodes resolve quicker in comparison with "endogenous" psychoses [52, 53, 199, 201, 202, 207–211] and do not recur unless cannabis use resumes [203], there is an emerging evidence suggesting that patients diagnosed with cannabinoid related AIPP are likely to develop a chronic recurrent psychosis that in our current nomenclature is classified as schizophrenia [195, 212–217]. Shorter (1 year) follow-up studies have suggested that substance-induced psychosis had similar levels of functioning, quality of life or relapse, and recovery rates compared to other psychoses [218] and that 25% of them were re-diagnosed to have primary psychosis at 1 year [213]. The percentage of patients initially diagnosed with cannabinoid-induced psychotic disorder later diagnosed with schizophrenia was found to range from as low as 3.87% [212] to 46% [217]. Recently, Alderson et al. (2017) [216] found a cumulative hazard for a diagnosis of schizophrenia of 17.3% over a follow-up period of 15.5 years; they further reported that the mean time for transition to a diagnosis of schizophrenia was around 13 years with 50 and 80% of them doing so within 2 and 5 years, respectively. Apart from male gender and younger age, longer (>2 weeks) first admission was found to be a risk factor for the transition [195, 216, 217]. The presence of family history of mental illness was also found to be a predictor [213].

Several large (n = ~20,000) recent studies in Northern Europe suggest that up to 50% of individuals without a pre-existing psychotic disorder who were initially hospitalized for ICD-10 cannabis-induced psychosis were re-diagnosed with a schizophrenia spectrum disorder during long-term (~8 years) follow-up [195, 217]; proportion increased to 75% when the diagnosis was expanded to *any* psychotic outcome [195]. Most recently, Starzer et al. (2017) reported outcomes in 6788 patients in Denmark who received a diagnosis of substance-induced psychosis over a 20-year period and who did not have any previous record of treatment for schizophrenia spectrum disorders or bipolar disorder [219]. One third of all patients with substance use-induced psychosis developed schizophrenia or bipolar disorder within 5 years. Notably, the highest risk of conversion to either schizophrenia or bipolar disorder was for patients who experienced cannabis-induced psychosis, which had a conversion rate of 47.4%. Collectively, these data would suggest that acute immediate persistent psychosis related to cannabinoids could be a harbinger of a more chronic recurrent psychotic disorder.

The tight temporal relationship between exposure and manifestation of psychotic symptoms, which resolves when cannabinoid use stops and recurs with the use of cannabinoids, provides compelling evidence for a causal relationship. However, the existing literature on cannabinoid-induced AIPP has several shortcomings. The premorbid status of individuals with AIPP was not carefully characterized. Furthermore, cannabis exposure was not confirmed by drug testing, and the dose of exposure was not carefully estimated. The contributions of other drugs or factors known to increase risk for psychosis was not carefully estimated. Furthermore, most studies which focused on positive symptoms, negative symptoms, or cognitive function were typically not assessed. In these limitations notwithstanding, the literature suggest that cannabinoids are associated with psychosis that manifests immediately after exposure, persists beyond the period of intoxication, and requires clinical intervention. Clearly further work is necessary to characterize cannabinoid-induced AIPP.

Chronic, Delayed, Persistent Psychosis (Schizophrenia)

Clinical Presentation

Exposure to cannabis in adolescence and adulthood has been reported to be associated with a chronic psychotic disorder (Fig. 14.1). This refers to psychosis that is chronic (continuous or episodic) and not time locked to acute toxic effects, i.e., it lasts beyond period of intoxication (persistent), occurs in the context of long-term moderate to severe cannabis use prior to onset of psychosis (delayed), and requires psychiatric intervention. The Swedish conscript study was one of the first studies to raise the link between exposure to cannabis and the risk of a chronic psychotic disorder (schizophrenia) [220–222]. All Swedish males conscripted into the military between 1969 and 1970, representing 97% (n = 50,053) of the population, aged 18 to 20 years were included in the cohort. In the initial report, those who reported using cannabis more than 50 times at conscription had a 6-time greater risk of developing schizophrenia relative to those who did not report using cannabis [220]. Subsequent reanalysis of the data re-estimated the magnitude of risk of schizophrenia related to cannabis exposure as lower in moderate users [222]. Further they report that odds ratios for developing schizophrenia, brief psychosis, and other non-affective psychosis were 3.7, 2.2, and 2.0, respectively, among frequent cannabis users compared with nonusers [222]. A dose-response relationship between self-reported cannabis and incident schizophrenia was noted [221].

Whether exposure to cannabinoids can "cause" chronic, persistent psychosis that is not time-locked to exposure is a subject of great interest and debate. Furthermore, whether the psychosis associated with cannabis exposure represents a distinct type of psychotic disorder that in our current knowledge base and diagnostic schema is categorized as schizophrenia is not clear. Currently, the diagnosis of schizophrenia is based on phenomenology and course, and it is conceivable like pneumonias which were eventually classified into subtypes, distinct, persistent, and recurrent psychotic disorders, that are currently lumped together as schizophrenia, e.g., 22q11.2 deletion syndrome and a cannabis-related subtype, will be identified on the basis of etiology and/or pathophysiology. Rounsaville (2007) speculated on a "cannabis-induced subtype of schizophrenia" [223] which he suggested could be differentiated "with [an] identification of early markers that clearly differentiate the 2 conditions and (b) more precise information about duration of psychotic symptoms induced by different substances" [224]. Some diagnostic systems list cannabis-induced psychosis as a distinct clinical entity in the existing psychiatric diagnostic systems. However, the validity of the diagnosis is uncertain.

Varma (1972) was one of the first to suggest the presence of a chronic persistent psychosis that was related to cannabis [225]. Varma screened 39,001 inpatients at a mental hospital in India over a period of 10 years and reported 1248 (3.2%) patients to be cases of cannabis psychosis; excluding cases where cannabis was merely incidental in the course of psychosis or a precipitating factor. Many (46.6%) of these cases of cannabis psychosis had a duration of 2 to 9 years of cannabinoid exposure prior to onset of psychosis. The illness was episodic (more than one episode, up to 7 episodes) in many cases (50.9%), with inter-episodic period lasting 1–2 years in 49.7% of cases. He reported that the cases had a characteristic phenomenology that included fluctuating reality contact, transient anger outbursts, aimless wandering for which the patient had insight, vivid visual hallucinations, emotional lability, non-genuine elation/euphoria, flight of ideas without coherence, and rapid fluctuations in speech intensity. However, this work has not yet been replicated, leaving questions about whether there is a distinct chronic persistent psychosis associated with cannabis exposure.

More recent studies have also attempted to further characterize cannabis-related psychosis (for review see Pauselli (2018) [226]. Caton et al. (2005) reported that patients with a psychotic disorder unrelated to cannabis have less insight and more severe psychiatric symptoms (positive, negative, general psychopathology). In contrast, those with cannabinoid-related psychosis were reported to have comorbid antisocial personality disorder, later age of onset of psychosis, visual hallucinations, and greater likelihood of more severe form of substance use disorder and more severe psychosocial problems [227]. Boydell et al. (2007) found a trend level distinction on better insight and fewer abusive or accusatory hallucinations in cannabis-related psychosis [228]. Rubio et al. (2012) reported that interpersonal sensitivity, depression, and phobic anxiety characterized cannabis-related psychotic disorder [229]. Baldacchino et al. (2012) concluded that patients with cannabinoid-related psychosis have more positive symptoms than those with psychosis in the absence of cannabis use [230].

Although cannabinoid use predicts development of psychotic disorder in those who have a positive family history of psychosis, a "positive family history" does not seem to distinguish CDPP from functional psychoses such as schizophrenia. Arendt et al. (2008), in a nationwide population-based sample of 2,276,309, found that risk of developing cannabis-induced psychosis and schizophrenia spectrum disorder in those with familial predisposition were similar in magnitude [231]. They reported that in children with a mother with schizophrenia, the risk of developing schizophrenia and cannabis-induced psychosis was 5- and 2.5-fold higher, respectively. Further, they reported that familial predisposition did not moderate the transition from cannabis-induced psychosis to a schizophrenia spectrum disorder and concluded that cannabis-induced psychosis could be an early sign of schizophrenia rather than a distinct clinical

entity. Similarly, Boydell et al. (2007) found few differences in phenomenology between schizophrenia patients who are cannabis users and nonusers [228]. They also found no differences in the proportion of individuals with a positive family history of schizophrenia between cannabis users and nonusers. They argued against a distinct schizophrenia-like psychosis caused by cannabis.

In contrast to the aforementioned studies suggesting that psychosis "caused" by cannabis is not a unique entity, other studies using more proximal measures of brain function, e.g., brain 18-FDG-PET [232] and prepulse inhibition of the startle response [233], found differences between cannabis using and non-cannabis psychotic disorder patients.

While the question of whether there is a distinct cannabis related chronic and persistent psychotic disorder needs further study remains unanswered, the question of whether cannabis confers risk for a chronic and persistent psychotic disorder seems to have greater support. There have been a number of cross-sectional and longitudinal studies attempting to replicate the findings of the Swedish study and also addressing its limitations [92, 94, 234–237] (Table 14.3). As reviewed recently by Gage et al., nine cohort studies, apart from the Swedish cohort, show a consistent pattern of an association between cannabis and psychosis [238]. However, only two of them have studied a syndromal diagnosis (either schizophrenia or schizophreniform disorder) as an outcome measure [212, 234]; others have used "psychotic symptoms" as outcome measures [238]. The magnitude of the risk of a chronic psychotic disorder (schizophrenia) conferred by cannabis is about two- to fourfold. Most studies have focused on positive symptoms, paying little attention to negative symptoms and cognitive deficits, which are important core symptoms of the schizophrenias. In longitudinal studies, the increased risk of developing psychosis associated with using cannabis persists despite adjusting for age, sex, social class, ethnicity, urbanicity, and use of other drugs. In one of the largest meta-analysis involving 66,816 individuals, a positive association between cannabis exposure and the risk for psychosis was confirmed with a twofold increase for the average cannabis user and a ~fourfold increase in risk for the heaviest users, relative to nonusers [239].

Longer-Term Effects of Cannabinoid Use on Negative Symptoms

Interestingly, an "amotivational syndrome" strikingly similar to negative symptoms of schizophrenia has been reported with chronic cannabis use [200, 203, 240–242]. This syndrome is characterized by apathy, amotivation, social withdrawal, narrowing of interests, lethargy, impaired memory, impaired concentration, disturbed judgment, and impaired occupational achievement. Interestingly, some recent studies report a transient "amotivational state" as acute effects of

Table 14.3 Longitudinal studies of cannabis as a risk factor for psychosis

Study	Country	Design	No.participants	Follow-up (years)	OR (95% CI) (adjusted risk)
Tien & Anthony	US	Population based	4,494	1	2.4 (1.2-7.1)
Zammit et al Manrique-Garcia et al	Sweden	Conscript cohort	50,053	27 35	3.1 (1.7-5.5) 1.8 (1.3-2.3)
van Os et al	The Netherlands	Population based	4,045	3	2.8 (1.2-6.5)
Weiser et al	Israel	Population based	9,724	4-15	2.0 (1.3-3.1)
Fergusson et al	New Zealand	Birth cohort	1,265	3	1.8 (1.2-2.6)
Arseneault et al	New Zealand	Birth cohort	1,034	15	4.5 (1.1-18.2)
Ferdinand et al	The Netherlands	Population based	1,580	14	2.8 (1.79-4.43)
Henquet et al	Germany	Population based	2,437	4	1.7 (1.1-1.5)
Wiles et al	UK	Population based	8,580	1.5	1.5 (0.55-3.94)
Rössler et al	Switzerland	Community Survey	591	30	1.8 (0.96-3.2)
Gage et al	UK	Birth cohort	1,756	2	1.1 (0.76-1.65)
Rognli et al	Sweden	Cohort of discharged prisoners	6,217	5	2.6 (1.40-5.0)
Bechtold et al	USA	Adolescent boys	1,009	5	1.51 (1.08-2.11)
					~2-fold increase

THC, as well [243]. Generally, polydrug use, poverty, low socioeconomic status, or pre-existing psychiatric disorders confound interpretation of such findings, and other investigators have argued that the syndrome does not exist.

Of note, consistent with the amotivational syndrome, as discussed earlier, the administration of THC to healthy humans in laboratory studies was shown to induce negative-like symptoms including blunted affect and emotional withdrawal.

While there is some phenomenological overlap, until there is a better understanding of the neurobiology underlying the negative symptoms of schizophrenia, it remains uncertain whether the amotivational syndrome associated with cannabis shares a similar neurobiology with negative symptoms of schizophrenia.

Longer-Term Effects of Cannabinoid Use on Cognitive Function

As discussed earlier, cannabinoids can produce acute transient impairments in cognitive function. A recent systematic review suggests that regular cannabis use is associated with mild cognitive changes, evidence for subtle cognitive deficits at least 7 days after heavy cannabis use [244]. Intriguingly, the profile of impairment observed in different cognitive domains is similar to that observed in schizophrenia [245].

Cognitive dysfunction associated with long-term or heavy cannabis use has been suggested to be a cognitive endophenotype of schizophrenia [168]. There are several studies suggesting that chronic, heavy cannabis use leads to impairments in memory, attention, working memory, executive function, and intelligence [246–255]. Broyd et al. (2016), in a recent review, concluded that verbal learning and memory and attention are most consistently impaired by chronic exposure to cannabis [120]. Although effects on learning and memory appear to recover, attentional and psychomotor dysfunction has been found to persist in chronic users and after cessation of use as well [120, 256]. However, there are anecdotal reports that suggest that impairments in verbal memory, attention, and some executive functions also may persist after prolonged abstinence [120]. Overall, proportion of cognitive domain impairment [120] reported is:

(i) Verbal learning and memory (27%)
(ii) Working memory (20.4%)
(iii) Processing speed (19.8%)
(iv) Reasoning and problem solving (15.2%)
(v) Attention (12.1%)
(vi) Visual learning and memory (5.5%)

Interestingly, from the prospective cohort of Dunedin's study, Meier et al., reported that chronic/persistent cannabis users or those with cannabinoid dependence syndrome showed significant neuropsychological decline from childhood to midlife [257]. They reported a decline of about 6 points (or approximately 8 points when dependence commenced in adolescence) in the intelligence quotient (IQ). Importantly, the loss of IQ did not restore despite cessation of cannabis use. Furthermore, the cognitive impairment is general, i.e., not specific to any particular cognitive domain. Furthermore, the findings suggest that when cannabis is used during specific stages of development, the consequences may be irreversible even though cannabis use may have ceased. However, recent reviews [120, 256] have challenged the findings of the Dunedin study.

Some studies suggest that CBD may protect against the negative effects of THC including its cognitive impairing effects. Although evidence for potential protection from cognitive effects by CBD continues to increase, it is premature to conclude that it has a definitive role in improving cognition in schizophrenia [120, 258].

Similar to phytocannabinoids, synthetic cannabinoid users also have cognitive deficits. Recently, Cohen et al. (2017) showed that they performed significantly worse than both recreational and non-cannabis users on executive function and long-term memory tasks [259]. Among predictors for a poorer cognitive outcome, younger age of onset has been consistently found to be associated [120].

Further, Schnakenberg Martin et al. (2016) showed that participants with high and moderate lifetime cannabis use had lesser impairment of neurocognition and metacognition compared to low lifetime cannabis use in psychosis [260]. Schizophrenia patients who abstained from cannabis after chronic abuse had greater improvements in verbal learning than in nonpsychiatric control abstainers [261].

Longer-Term Effects of Cannabinoid Use on Electrophysiological Indices of Information Processing

As discussed earlier, acute administration of cannabinoids has been shown to produce deficits in a number of electrophysiological indices of information processing also known to be abnormal in schizophrenia, e.g., P300, gamma oscillations. Cannabinoids are also known to be associated with longer-term electrophysiological indices of information processing also known to be abnormal in schizophrenia.

The P50 response, a measure of auditory sensory gating has been shown to be disrupted in patients with schizophrenia [168, 169, 262–264] and by cannabinoid agonists acutely in rats [265, 266]. Deficits in P50 suppression have been reported in chronic cannabis users [267, 268]. Emerging data (unpublished data: Skosnik et al.) suggest that THC acutely reduced P50 suppression in healthy subjects.

Mismatch negativity (MMN) is an automatic, preattentive ERP component representing basic auditory information processing and sensory memory [269, 270] that is shown to be reduced in patients with schizophrenia, early psychosis, and individuals at high-risk for psychosis [271, 272]. While in the only acute study conducted, oral THC did not affect MMN amplitude [273], chronic cannabis users have decreased MMN amplitudes [274–276].

Acute administration of THC in experimental conditions has been found to decrease theta oscillatory activity, in terms of resting state power that correlated with working memory deficits or phase-locking factor evoked by working memory tasks [170, 176, 177, 179, 180]. Acute administration of THC has also been shown to dose-dependently reduce steady-state gamma oscillatory power, which was related to psychotomimetic effects of it [277].

Finally, chronic cannabis users have been reported to show deficits in neural oscillations in the beta (13–29 Hz) and in the gamma range (30–50 Hz) which showed a significant association with schizotypy scores or early age of onset [278–282].

Relationship between Cannabis and Psychosis: Factors Indicating Causality

Major factors that seem to increase the risk for development of psychosis related to cannabis include an earlier age at onset of cannabis use [283] and higher levels of cannabis use [220–222, 239, 284–286]. While "earlier age at onset of cannabis use" outlines "temporal relationship" or the "directionality" in the relationship between cannabis use and psychosis, "higher levels of cannabis use" asserts the dose response.

The criteria used to establish disease causality include direction, temporality, strength of the association, dose response or biological gradient, specificity, consistency, experimental evidence, and biologic plausibility [287, 288]. While experimental evidence has been described in detail under clinical presentation, each of the other criteria establishing a "causal" relationship is elucidated here.

Direction and Temporality

The preliminary analysis of the Swedish conscript study [220, 221] found that the relative risk for schizophrenia was significantly higher in those who developed schizophrenia within 5 years of conscription, which raises questions about the direction of causality. In other words, this preliminary analysis could not distinguish whether cannabis use led to schizophrenia or whether subjects used cannabis in an attempt to self-medicate incipient symptoms of schizophrenia. In a secondary analysis that excluded those who developed a diagnosis of schizophrenia within 5 years of conscription, the adjusted relative risk remained significant only for those who had used cannabis more than 50 times [222].

Kuepper et al. (2011) [236], who used in-person interviews in the assessment of 923 individuals from the general population (aged 14–24 years), showed that cannabis use was associated with an increased risk of psychotic symptoms and persistent use increased this risk further. This is in contrast with another Ferdinand et al. [289], which showed the relationship to be bi-directional, alluding to the possibility of a phenomenon of "self-medication."

Similar to the findings from Varma (1972), many retrospective studies have found cannabis use to precede the development of psychosis by a period of years in first-episode psychosis (FEP) patients with a history of cannabis exposure [290–292]. These reports have also been supported by the findings of a number of earlier longitudinal, prospective studies [293–296].

In more than 60% of patients diagnosed with comorbid cannabis use disorder along with schizophrenia, the onset of substance use is before the onset of illness [297–301]. A recent meta-analysis showed that the interval between initiation of regular cannabis use and age at onset of psychosis was 6.3 years [302]. Among first-episode schizophrenia patients, about three fourths of cannabis users had the onset of cannabis abuse before the onset of positive symptoms [303]. Among various substances of abuse, cannabis has been found to be associated with an earlier onset of psychosis compared to other drugs/substances [304]. Specifically, age at onset of schizophrenia has been found to be nearly 2–3 years earlier in patients with comorbid cannabis use disorders compared to nonusers, after controlling for various confounding factors [304, 305]. Further, it has been suggested that age at onset of cannabis use moderates the link between cannabis and psychosis, especially schizophrenia [306]. However, it is important to note here that younger age at presentation has not been found to be significantly associated with positive symptoms, negative symptoms, and daily functioning [307]. An important factor related to earlier onset of both substance use and psychosis is increased genetic vulnerability [297, 300]. Interestingly, in the subset of patients with comorbid cannabinoid use disorder, males have an earlier age of onset than females [304, 308]. Interestingly, Frascarelli et al. (2016) found an interactive role of poor premorbid school adjustment but not age or positive family history for psychiatric illness in the early onset of psychosis in patients using cannabis use before onset of psychosis [309].

However, it should be noted that the onset of a psychotic disorder such as schizophrenia psychosis may occur well before the onset of psychosis, i.e., the onset of psychotic symptoms in schizophrenia may merely be the first obviously recognizable

symptom of the disorder. This needs to be accounted for in any discussions regarding the temporal relationship between exposure to cannabinoids and onset of illness.

Strength of Association

Moore et al. (2007), in a systematic review and meta-analysis, found that the association between cannabis and later psychotic outcomes is modest [285], approximately twofold. To put the strength of the association in perspective, even though cigarette smoking is well recognized as being associated with a greatly increased risk for lung cancer, relative to never-smokers, the absolute lifetime risk of a smoker developing lung cancer is approximately 10% to 20% [310].

In addition to observational studies, others have investigated the genetic relationships between cannabis and schizophrenia and reported that a genetic risk score for schizophrenia predicted cannabis use. Common genetic variants underlying schizophrenia and lifetime cannabis use seem to overlap, in part. Thus, individuals with a stronger genetic predisposition to schizophrenia are more likely to initiate cannabis use, use cannabis more regularly, and consume more cannabis over their lifetime [311, 312]. These findings could be interpreted as shared genetic etiology but could also reflect a causal association between schizophrenia and risk of cannabis use. Another approach that may allow causal inference from observational data is Mendelian randomization. Two recent studies, using the Mendelian randomization study, assessed the strength of causality. While Vaucher et al. (2017) [313] reported that use of cannabis was associated with increased risk of schizophrenia with an odds ratio of 1.37, Gage et al. (2017) [314] reported an odds ratio of 1.10 per doubling of the odds of schizophrenia.

Further, Giordano reported that increasing the temporal delay between cannabinoid exposure and onset of schizophrenia significantly attenuated the strength of association of the risk [315].

Dose Response/Biological Gradient

Most large epidemiological studies have found a consistent dose response in the association between cannabis and psychosis [92, 220, 222, 235, 316]. In general, those who report heavier cannabis use have a higher risk of a psychosis outcome. Notwithstanding these findings, it should be noted that there are considerable challenges to establishing a dose-response effect. Estimating cannabis use is fraught with problems given that the units of use vary considerably: joints, bongs, bowls, etc. The concentration of THC in cannabis, which contributes to the dose of exposure, varies significantly and is not measured in most studies. Furthermore, the concentration of CBD, which is believed to offset the pro-psychotic effects of THC [317], can also vary and is not measured in most studies.

The greater the quantity of cannabis used, the greater the risk for psychosis. The definition of "greater quantity" varies across studies from "high consumers," i.e., use on more than 50 occasions [220–222], to "most frequent use," i.e., daily use > weekly use, or "dependence" [285]. Kelley et al. (2016), in a retrospective assessment of premorbid cannabinoid use from age of 12 until the onset of psychosis in a sample of first-episode patients, reported that escalation of premorbid use in the 5 years prior to the onset of psychosis was highly predictive of an increased risk for onset [318]. A recent meta-analysis by Marconi et al. (2016) plotted the risk of schizophrenia and other psychosis outcomes among the most severe cannabis users compared to the nonusers and showed that while the risk is doubled in any or median users, it is quadrupled in most severe users [239]. Furthermore, while the risk of schizophrenia over the decades decline in moderate users, the decline is significantly attenuated in frequent users [222].

Specificity

Specificity of the Association between Psychosis and Cannabinoids Versus Other Drugs

There are challenges to studying the specificity of the association between psychosis and cannabis because individuals who use substances often use more than one substance, making attribution of causality more challenging. In one large study [217], the conversion to schizophrenia was reported to be highest with cannabis (46%) followed by amphetamines (30%) and alcohol (5%) suggesting a greater specificity of psychosis outcomes than for other substances; this was also reported by some [234, 235, 319] though not all [212, 320] studies. Sara et al. (2014) reported that while cannabis disorders predicted an increased likelihood of progression to schizophrenia, stimulant-use disorders predicted a reduced likelihood [215]. Giordano et al. (2015) showed that, apart from cannabinoid use disorder, abuse of opiates, sedatives, cocaine/stimulants, and hallucinogens was also strongly associated with subsequent schizophrenia in the general population. However, after controlling for familial confounding, among other substances, only cocaine/stimulant use remained associated [315].

While there is a strong association between cigarette smoking and schizophrenia, there is little evidence to support the notion that cigarette smoking, unlike cannabinoids, *causes* either (1) acute transient psychosis, (2) a chronic psychotic disorder such as schizophrenia, or (3) exacerbates psychosis in patients with a psychotic disorder. On a related note, while cannabis exposure is associated with an earlier age of onset of psychosis – by 2.7 years in one meta-analysis

[321] – cigarette smoking which is also highly prevalent in psychotic disorders is not associated with an earlier onset of psychosis [322]. Importantly, it has been argued that attempts to understand the association of psychosis with cannabis use versus cigarette use may be futile as rates of co-occurrence are significantly high [323].

A recent study reports that about 50% of cannabis use disorder patients present with polysubstance use disorder and that they had worse psychotic and functional outcomes [324]. Interestingly, co-use of other substances has been shown to have a confounding effect specifically on the influence of cannabis on hallucinations [325].

Experimental studies may complement observational studies in determining the specificity of the association between cannabis and psychosis. Thus, as discussed previously cannabinoids have been demonstrated to induce an array of psychosis-related phenomena in healthy individuals and exacerbate symptoms in individuals with schizophrenia. Similarly, stimulants (amphetamine, methylphenidate), ketamine, and serotonergic hallucinogens have also been shown to produce some psychosis-like effects in healthy individuals and exacerbate symptoms in individuals with schizophrenia. However, nicotine, opioids, and alcohol do not really induce psychosis-like effects or exacerbate psychosis in individuals with psychotic disorders.

Specificity of the Association between Cannabinoids and Psychosis Versus Other Neuropsychiatric Disorders

The contribution of "cannabis use" in causing other neuropsychiatric disorders is far less studied than for psychosis. Moreover, there are no head-to-head comparisons between psychotic disorders and other neuropsychiatric disorders. The limited literature on the association between cannabis and mood and anxiety disorders is inconsistent. Brook et al. (2002) found that earlier cannabis use significantly predicted later major depressive disorder, alcohol dependence, and substance use disorders in their late 20s [326]. van Laar et al. (2007) showed that any use of cannabis at baseline predicted a modest increase in the risk of a first major depression (odds ratio – 1.62) and a stronger increase in the risk of a first bipolar disorder (odds ratio – 4.98), despite controlling for strong confounders [327]. A systematic review and meta-analysis of longitudinal studies by Lev-Ran et al. (2014) [328] reported that the odds of developing depression in cannabis users compared to controls was 1.17.

Manrique-Garcia et al. (2012), in a longitudinal study of a national cohort of Swedish conscripts, found an increased risk of schizoaffective disorder (in line with psychosis) but did not find evidence for an increased risk of depression among those who used cannabis [329]. Degenhardt et al. (2013) [330] studying persistence of the association between adolescent cannabis use and common mental disorders into young adulthood found that daily cannabis use was associated with anxiety disorder (odds ratio – 2.5); however, they could not find consistent associations between adolescent cannabis use and depression. Blanco et al. (2016) [331], who analyzed interviews of 34, 653 individuals, reported that cannabis use was significantly associated with later development of any –or other – substance use disorders but not any mood disorder or anxiety disorder.

Experimental studies may complement observational studies in determining the specificity of the association between cannabis and psychosis. Thus, as discussed previously, cannabinoids have been demonstrated to induce an array of psychosis-related phenomena. In experimental studies, cannabinoids may have bidirectional effects on anxiety – producing anxiolysis at some doses and in some individuals – but occasionally producing anxiogenic and even panic-like effects. In general, cannabinoids do not appear to induce depression in experimental studies; rather they produce transient euphoria.

Biological Plausibility

The precise mechanisms by which cannabinoids *cause* acute or persistent psychosis are not known. It is likely that different mechanisms may play a role. Several plausible biological mechanisms have been proposed by which cannabinoids might induce psychosis.

In several brain regions, particularly the cerebral cortex and hippocampus, CB1Rs are present on the axon terminals of cholecystokinin (CCK) containing GABA interneurons that target the perisomatic region of pyramidal cells (PCs) [332]. CB1Rs are also located on glutamatergic neuron. CB1-Rs are activated by endocannabinoids released postsynaptically by depolarized pyramidal cells [333]. The activation of CB1Rs inhibits the release of GABA by CCK-basket cells (BCs) leading to a disinhibition of postsynaptic PCs [334]. Thus, a CB1-R-mediated braking mechanism regulates the timing and release of GABA and subsequently the overall inhibitory/excitatory balance in cortical networks [335]. This interplay between GABA, glutamatergic, and CB1R systems may provide a mechanism by which cannabinoids upset the fine balance between inhibitory and excitatory neurotransmission; there would be disinhibition and desynchronization of pyramidal cell activity and alterations in synchronized neural oscillations, leading to perturbations in gating, associative functions, and neurocognition, which could culminate in psychotic symptoms. As discussed earlier, cannabinoids have been shown to disrupt neural oscillations in the theta and gamma range in humans. Such a mechanism might also explain why individuals with schizophrenia who already have GABA deficits may be more vulnerable to the acute effects of cannabinoids.

While the acute effects of cannabinoids on DA, GABA, and glutamate neurotransmission may explain some of the acute positive, negative, and cognitive symptoms of cannabinoids, the mechanism by which exposure to cannabinoids might *cause* a psychotic disorder (such as schizophrenia) that is recurrent and that persists well beyond the window of exposure has not yet been established. If schizophrenia is a neurodevelopmental illness [336, 337], then the observation that early cannabis exposure is associated with a greater risk for the development of schizophrenia may offer some clues to the underlying biological mechanisms. Consistent with the human epidemiological data, animal studies suggest that early (adolescent) but not later (adult) exposure to cannabinoids is associated with persistent impaired social behaviors, including psychotic-like behaviors and cognitive and sensorimotor gating deficits in adults [338–342].

Adolescence and young adulthood are critical phases for brain development which continue into young adulthood (up to 25 years) [343]. Therefore, any factors that interfere with brain development during this time may have far-reaching consequences. During this period of neuronal plasticity, there is sprouting and pruning of synapses, myelinization, and changes in neurotransmitter concentrations and their receptor levels in brain areas necessary for behavioral and cognitive functions [344]. The endocannabinoid system plays an important role in several processes important in neurodevelopment including neurogenesis, neural specification, neural maturation, neuronal migration, axonal elongation, glia formation, and positioning of inhibitory GABAergic interneurons and excitatory glutamatergic neurons [345–353]. Perturbation of the endocannabinoid system in the rapidly changing brain, as is the case in adolescence, by nonphysiological stimulation, as may be the case with exposure to exogenous cannabinoids, may have far-reaching consequences. This would be especially so in the presence of already altered neurodevelopmental processes. Therefore, by disrupting the endocannabinoid system and interfering with neurodevelopmental processes, exogenous cannabinoids may provide a biologically plausible mechanism by which exposure to cannabinoids during adolescence may increase the risk for the development of schizophrenia.

Relationship between Cannabis and Psychosis: Factors that may Influence Vulnerability

Age of Initiation of Cannabis Use

While adolescent onset of exposure to cannabis is associated with a higher risk for development of psychosis, the risk has been found to decline when exposure is after late adolescence. One study reported that the association between cannabis and psychotic disorders was only significant when cannabis use began before age 14 [291]. Another study found that, compared to cannabis users with onset after age 17, those who began use before age 17 had a significantly greater risk of positive symptoms and a greater risk of auditory hallucinations [354]. One interpretation of these findings is that cannabis exposure during critical periods of brain development may lead to long-lasting consequences by altering brain development. Indeed, this hypothesis has received some support from animal studies which show that exposure to cannabinoids in adolescence has more deleterious effects than exposure in adulthood [338–342]. On the contrary, Kelley et al. (2016) found that the strength of the association was similar among those who used cannabinoids before the age 17 and those who used it after the age 17, suggesting that cannabinoid use in young adults is as important as in adolescents [318].

Genetic Factors

Emerging evidence suggests that polymorphisms of certain genes related to dopamine metabolism, e.g., COMT, AKT1, DAT1, NRG1, and BDNF, may moderate the effects of cannabis on psychosis. (For review see Radhakrishnan et al. (2014) [254].) Interestingly, these genes have been considered as historical candidate genes for schizophrenia [355].

While studies consistently report a three-way interaction of COMT (Val allele) gene polymorphisms with cannabis use, childhood abuse, and risk for psychosis [356, 357], evidence for a direct relationship between COMT polymorphism and cannabis-related psychosis is inconclusive. Although initial evidence suggested that the relative risk of developing psychosis in cannabis users is dependent upon COMT polymorphisms [191, 358, 359], studies conducted later report no such mediation [360–365]. However, this genetic polymorphism has been found to be associated with early age of onset of psychosis [361, 366].

AKT1 gene polymorphisms, both C/C and G/G alleles, have been implicated to have a mediating role between cannabis use and development of psychosis [365, 367, 368]. Recently, AKT1 risk alleles have been shown to increase the incidence of cannabis use in already diagnosed patients with a psychotic disorder [369]. DAT1 gene (the nine-repeat allele) polymorphism has also been found to involve in the mediation between cannabis use and psychosis [367]. A synergistic interaction between DAT1 and AKT1 gene polymorphisms on development of psychosis in cannabis users has also been reported [367].

Although evidence from animal studies suggest a mediating role of NRG1 on cannabis use and psychosis [370], no human experiments on this gene marker have been conducted, as yet. Compared to Val/Val genotypes, Met carriers of BDNF gene with cannabis use have been shown to be

associated with early onset of psychosis; this relationship was restricted to females [371].

Family Predisposition

Heritable factors have been suggested to attribute about 50–70% of the variance between cannabis use disorders [372]. Very recently, in a twin study using "co-twin control" analysis to investigate effect of familial confounding for the association between cannabinoid-use disorder and psychotic-like experiences, Nesvåg et al. (2017) [373] showed that the heritability estimates for cannabinoid use disorder were significant (88% in men and women) and 77% in men and 43% in women, respectively, for psychotic-like experiences. The genetic and environmental correlations between symptoms of cannabinoid use disorder and psychotic-like experiences were 0.55 and 0.52, respectively. This study also showed that the association between cannabinoid use disorder and psychotic-like experiences could be explained by shared genetic and environmental factors and direct effects from cannabinoid use disorder. Intriguingly, Giordano et al. (2015) showed that strength of association between cannabinoid use and later onset of schizophrenia reduced three- to fivefold than the population-based estimates, when controlled for degrees of familial confound [315].

Childhood Maltreatment

Measures of environmental risk, such as childhood adversity, have been suggested to provide promising new leads in the understanding of the association between cannabinoid exposure and the development of psychosis [372]. While Houston and colleagues found an odds ratio of 11.96 (95% CI 2.10–68.22) for having experienced psychosis among children with a history of abuse who used cannabis prior to age 16 [374], Harley et al. reported an odds ratio of 20.9 (95% CI 2.3–173.5) for experiencing psychosis in adolescents with a history of exposure to trauma and cannabis [375]. Konings et al., in a population-based longitudinal study, replicated the assertion that a significant interaction exists between cannabis use and childhood maltreatment in the development of psychotic symptoms [376]. Kuepper et al., however, could not replicate these findings [377].

Urbanicity

Although anecdotal, there is evidence suggesting a relationship between urbanicity, cannabinoid use, and persistent psychosis. Kuepper et al. (2011) showed that individuals living in an urban environment are more likely to use cannabinoid and also that the association between cannabinoid use and psychotic symptoms was much stronger in those from an urban habitat [378]. Cougnard et al. (2007) found that the cannabinoid use, childhood trauma, and urbanicity, additively, increase the risk of persistent psychosis in individuals with baseline transient psychotic experiences [379].

The Effects of Cannabinoid Use Across the Stages of Illness and Spectrum of Symptoms

This section is intended to reflect the role of cannabis use in those at high risk for psychosis, first-episode psychosis, or established schizophrenia.

Prodromal Symptoms

Cannabis use has not only reported to precede the onset of psychosis but also the prodrome of schizophrenia [380–382]. While, Goldberger et al. (2010) found that cannabinoid use before prodromal symptoms was seen in 35% patients with schizophrenia [381], Leeson et al. (2012) reported a gap of 6 years between average age of onset of cannabinoid use and prodromal symptoms [382]. Bechtold et al. (2016) reported that adolescents who regularly use cannabinoids were at a heightened risk of developing subclinical psychotic symptoms and that these symptoms persisted even when they stopped using cannabinoids for a year [383]. Among (ultra-high risk) UHR individuals, cannabis users have been shown to have higher rates of unusual thought content and suspiciousness than nonusers [384]. McHugh et al. (2017) reported that ultrahigh risk (UHR) for psychosis with cannabis-induced APS was ~5 times more likely for transition into a psychotic disorder [385]. A recent meta-analysis has shown that cannabis use was predictive of transition to psychosis in those who met criteria for cannabis abuse or dependence, suggesting a dose-response relationship [386].

Experimental Evidence

Recently, Vadhan et al. (2017) examined the acute effects of smoked marijuana (5.5% Δ9-THC) under controlled laboratory conditions in cannabis using individuals who were clinically at high risk for psychosis. They reported transient increases in paranoia, anxiety, slowed time perception, visual illusions, feelings of strangeness and inattention, and neurocognitive (working memory and response inhibition) impairments during cannabis intoxication [387]. Interestingly, the controls (cannabis users not at clinical high risk) did not show such impairments.

Duration of Untreated Psychosis

A systematic review and meta-analysis by Burns (2012) suggest a nonsignificant trend level relationship between cannabis use and shorter duration of untreated psychosis [388]. Indeed, Broussard et al. (2013) has reported that having ever used cannabis, not necessarily heavy usage or usage in dependence pattern, had a significant relationship with dura-

tion of untreated psychosis [389]. Contrariwise, Green et al. (2004) showed that psychosis in cannabis users had a longer duration of untreated psychosis [390].

Interestingly, a study on bipolar disorder shows that longer duration of untreated first-episode mania was associated with risk of excessive cannabis use after onset of the bipolar disorder [391].

Established Schizophrenia

Some of the material presented below has been addressed in earlier sections but are included along with other information for completeness.

Positive Symptoms

While comparing patients of schizophrenia with comorbid cannabis use disorder and those without, most studies have found that the former group reported significantly greater positive symptoms [297, 303, 390, 392, 393] with more severe hallucinations [303, 392] and delusions [303] than the latter. However, a few studies have failed to demonstrate statistical differences between the groups on positive symptoms [300, 394–397]. Confounders identified in studies with negative results include heterogeneity in the course of illness (chronic vs. first-episode psychosis), severity of cannabinoid use (abuse vs. dependence; any use vs. heavy use), effect of other co-used substances, etc. Experimental studies discussed earlier show incontrovertible evidence that cannabinoids worsen positive symptoms in individuals with schizophrenia.

Negative Symptoms

There is a lack of consensus regarding the impact of cannabinoid use on negative symptoms. While, there is evidence in favor of significantly lower negative symptoms in patients of schizophrenia with comorbid cannabis use disorder [297, 390, 395, 396] (specifically, alogia [395]), some studies have failed to demonstrate such results [394, 397]. Correspondingly, while some studies have reported less severe depressive symptoms [300], others have found greater depressive symptoms in this population [393]. One experimental study discussed earlier showed that THC increased negative symptoms in individuals with schizophrenia.

Cognitive Symptoms

Studies of cognitive function in cannabis-using patients with schizophrenia have yielded intriguing results that seem counterintuitive. While D'Souza et al. (2005) clearly show that cannabinoids *acutely* worsen cognitive test performance in individuals with schizophrenia, and that schizophrenia patients are more vulnerable to the memory impairing effects of cannabinoids, several cross-sectional studies suggest that patients with psychosis and comorbid cannabis abuse have better cognitive performance than patients without comorbid cannabis abuse [261, 394, 398–400]. These findings seem counterintuitive given that acute cannabinoids disrupt cognition as shown in studies of animals, healthy humans, and schizophrenia patients. Furthermore, cognitive function in cannabis users (not diagnosed with psychosis) tends to be worse. Wobrock et al. (2013) specifically found better performance in psychomotor speed [394]. In contrast, Waterreus et al. (2017) reported that in individuals with a psychotic illness, cognitive function did not differ between current, past, and nonusers of cannabis [401]; however, current cannabis users with affective psychoses had worse cognition than cannabis users with non-affective psychoses. Helle et al. (2017) reported that better social cognition does not moderate the relationship between cannabis use and better executive function [400]. While these cross-sectional studies suggest that cognitive test performance is better in cannabis-using patients with schizophrenia, whether this reflects better premorbid function or is secondary to cannabis use is not clear. Future studies taking into account premorbid differences in cognitive test performance may need to be conducted.

Course and Functional Outcome

Short term (6–12 month) course analysis showed that cannabis use in the course of psychosis is related to poorer psychosocial functioning [393], especially when related to a lifetime history of cannabinoid use disorder [402]. Subclinical depressive symptoms have been found to be significantly associated with continued abuse of cannabis during treatment follow-ups and hence with worse functioning [403]. Intriguingly, this relationship between substance use and clinical functioning has been found to be restricted to schizophrenia patients and not with affective psychosis [402]. Finally, in schizophrenia, cannabinoid use disorders were significantly associated with increased risk of all-cause mortality (Hazard Ratio 1.24) [404].

Effect of Abstinence

While one study reported that discontinuing cannabis use was associated with better outcome in terms of lesser positive symptoms, better global functioning, and lesser psychotic relapses than persistent use [309, 371–373], other studies report the impact of abstinence to be on ancillary symptoms like anxiety and functioning but none on psychotic symptoms [374]. Interestingly, from the prospective cohort of the Dunedin study, Meier et al. [256], loss of IQ observed in cannabis users did not restore despite years of abstinence from cannabis. Clearly, further research is necessary to determine whether there is recovery from the negative consequences of cannabis with abstinence.

Treatment

McLoughlin et al. (2014) [405], in their meta-analysis, found four types of interventions targeted to reduce cannabis use – (1) adjunct psychological therapies versus treatment as usual, (2) adjunct psychological therapy versus adjunct non-specific psychoeducation, (3) antipsychotic versus antipsychotic, and (4) cannabinoid versus antipsychotics. They concluded that none of the interventions were better than each other in reducing cannabis use.

Specifically considering cannabis use among people with psychotic disorders, a systematic review by Baker et al. (2010) [406] suggested that that effective treatment of the psychotic disorder with standard antipsychotics is associated with reduction in cannabis use. More importantly antipsychotic treatment was not found to be associated with a worsening of cannabis cravings or use [407]. Recent evidence suggests that clozapine, compared other antipsychotics, was better in reduction of cannabis use in adolescents with psychotic disorders [408]. More evidence is, of course, required to make any kind of generalizations.

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Medical Consequences of Cannabis Use

15

Jag H. Khalsa and Ruben Baler

Introduction

In 2016, according to nationally representative data, approximately four million Americans age 12 or older met criteria for a cannabis use disorder (CUD), the complex phenomenon whose many facets are aptly explored in other chapters of this book. However, since current cannabis users outnumber those who develop a CUD by a factor of around six [2], it is important to identify, study, and mitigate any adverse health effects of cannabis use that may end up affecting a significantly larger fraction of the population, and not just in the United States. Indeed, it is estimated that close to 180 million people worldwide (or 2.5% of the total population) [148] are regular consumers of cannabis, an annual prevalence that is over 12-fold higher than that of cocaine or opiates. The lopsided ratio between the sizes of the nonaddicted and the addicted cannabis-using populations is reminiscent of comparable relationships among users of tobacco and alcohol. The hard lessons we should have learned from the devastating toll of licit drug use over past decades should help us focus our public health attention on the potential impact of regular cannabis use on morbidity and mortality among large pools of nonaddicted individuals. Even if the recognized non-CUD adverse health effects of cannabis prove marginal or linked exclusively to high frequency/potency, early onset, or heavy use, the sheer number of exposed individuals (including to second-hand smoke), combined with increased social acceptance and more permissive policies, makes the topic of this chapter a critical public health matter. This is particularly true when we consider that specific subpopulations, such as the developing fetus or adolescents, older adults, and those suffering from other physical (e.g., HIV) or mental (e.g., schizophrenia) disorders, are likely to present a significantly higher vulnerability to specific adverse effects stemming from cannabis use.

Cannabis contains many phytocannabinoids, but THC is the one primarily responsible for the *psychoactive* effects sought by cannabis users. The adverse health effects that are the focus of this chapter, however, present a more complex picture for they can result not only from the action of specific phytocannabinoids (THC and others) but also from exposure to other compounds present in the plant or produced during its combustion [109], or to a growing family of synthetic derivatives with cannabimimetic effects [25, 75, 76]. Activation of the endocannabinoid system (ECS) by THC and related molecules results in a variety of clinical effects as broadly outlined by the World Health Organization (WHO) [148], while cannabis smoke has been shown to contain many of the toxins, irritants, and carcinogens that are present in tobacco smoke [109].

Not surprisingly, the use of cannabis has been associated with a wide range of medical consequences affecting almost all physiological systems. Thus, medical consequences of cannabis use have been frequently reported in the scientific literature, whether through case reports, ecological studies, or meta-analyses [57, 106]. The cumulative body of work leaves no doubt that cannabis use, particularly if it is heavy, frequent, or long-term, is associated with increased risk of specific clinical conditions. However, the strength of the underlying evidence is decidedly mixed, likely because, in most cases, the size or rarity of the observed effects combines with a long list of confounding factors to make the attribution of generalizability, mechanisms of action, and causal relationships very difficult to ascertain. Such caveats notwithstanding, there is clear consensus that cannabis use can affect the respiratory and cardiovascular systems, in ways that could require clinical

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care. Here, we review the state of the science on these and other, somewhat less well-documented potential or alleged medical consequences of cannabis use.

Respiratory/Pulmonary Complications

Given the overwhelming evidence linking tobacco smoke to multiple respiratory conditions, it would be reasonable to predict that regular inhalation of cannabis smoke be associated with a similar pattern of adverse environmental exposure consequences. The truth is that we know less than we would like to about the specific attributable effects of cannabis on pulmonary function. With the exception of the active ingredients (i.e., cannabinoids [40] and nicotine, respectively), cannabis smoke is known to contain many of the 6000 chemicals (e.g., carbon monoxide, vinyl chlorides, ammonia, acetaldehyde, formaldehyde, acrolein, phenols, nitrosamines, reactive oxygen species, and polycyclic aromatic hydrocarbons) found in tobacco smoke [69, 101, 113], some of which have carcinogenic or other harmful effects [67, 112]. Although far fewer cannabis than tobacco cigarettes are generally smoked daily, the pulmonary consequences of smoking cannabis could theoretically be magnified by the greater deposition of smoked particles in the lung due to the deeper and more protracted nature of inhalation that is typical of cannabis compared to tobacco smoking styles. Indeed, according to an early study, smoking one cannabis joint leads to a higher pulmonary burden of insoluble particulates (tar) and carbon monoxide than smoking one cigarette with an equivalent amount of plant material (i.e., tobacco) [152]. This hypothesized differential in toxicant burden seems consistent with the results of a recent animal study showing cannabis smoke being significantly more potent than tobacco smoke in inducing severe (and CB1 independent) airway hyperresponsiveness, inflammation, tissue destruction, and emphysema [64]. However, even though cannabis smoke contains as many or perhaps more toxic, carcinogenic, and cocarcinogenic chemicals than tobacco smoke [66, 137], such as 50% more benzopyrene and nearly 75% more benzanthracene, on a gram-per-gram basis [137], the risks of pulmonary complications in humans appear to be relatively small and far lower than the devastating pulmonary outcomes caused by chronic tobacco smoking, particularly among occasional users with low cumulative doses [106]. Unfortunately, we still have a poor understanding of the underlying pathophysiology of the adverse respiratory/pulmonary effects of cannabis smoking, for which there is limited, let alone convincing, evidence, as described below.

Regular exposure to cannabis smoke may lead some smokers to experience airway inflammation [87, 128], explaining why regular smokers of cannabis are likely to experience chronic cough and produce larger than normal amounts of phlegm [95]. A critical analysis of all the available data found substantial evidence that long-term cannabis smoking can result in symptoms of bronchitis [106]. While the accumulated evidence regarding pulmonary function appears to point to a substantial association, the effect size may be quite modest. For example, a 2015 cross-sectional study of 12,500 patients attending a Scottish general practice found that, while the cannabis-using group did display impaired lung function, that impairment, after adjusting for confounders, consisted of a 0.3% increase in the prevalence of chronic obstructive pulmonary disease (COPD) for each additional joint-year of cannabis use [93]. Another cross-sectional study of US adults (data from the 2007–2010 National Health and Nutrition Examination Survey combined cohort) found that exposures of up to 20 joint-years were not associated with adverse changes in spirometric measures of lung health [79].

Such modest effects notwithstanding, analysis of bronchoscopic biopsies taken from cannabis smokers often show histological changes in the bronchial mucosa [44] that are accompanied by increased expression of a panel of cell proliferation biomarkers (e.g., EGF, p53, erbB-2) commonly used as reliable correlates of field cancerization effects on bronchial epithelium [13]. And yet, there is no conclusive evidence that cannabis smoking is associated with an increased incidence of lung cancer. In fact, a combined analysis of the six highest quality case-control studies of 2159 cancers and 2985 controls by the International Lung cancer Consortium [153], yielded an overall pooled odds ratio (OR) for habitual versus nonhabitual cannabis users or never-users of 0.96. Thus, the best available information does not support an association between cannabis use and lung cancer [68]. Another conclusion to come out of a recent meta-analysis pertains to the lack of evidence of an association between cannabis use and increased risk of developing or exacerbating symptoms of asthma [106]. These results are surprising, given that wheezing and other asthma-like symptoms are rather common among regular cannabis users, but the picture could still change once larger and better designed/controlled studies (including monitoring adherence to asthma medications) are implemented. However, they are consistent with the results of a recent reanalysis of the Dunedin birth cohort, which showed that, up to 20 years of cannabis use, unlike tobacco, was not associated with worse lung function, systemic inflammation, or metabolic health at age 38 [96].

The reasons behind these apparent paradoxes, above and beyond fundamental flaws in study design or power, are not fully understood, but some authors have speculated that THC's activity as a bronchodilator [138, 139] and/or the observed anti-inflammatory effects of cannabis [136] may be at least partly responsible [123]. Another possibility worth exploring is the alleged ability of some cannabinoids (both

endogenous and plant-derived) to inhibit growth or trigger programed cell death among some cancer cells [34, 45]. This or other cannabis-specific confounding factors may also help explain the moderate but unexpected evidence of a statistical association between cannabis smoking and *higher* forced vital capacity (FVC) [79] and the *positive* effect of acute but not chronic cannabis use on airway dynamics [106].

The last point suggests that future research that pays closer attention to dosage as a variable could expose more robust effects that have laid hidden in cross-sectional studies, studies with small Ns, or studies that were based on traditionally low (and increasingly dated) or heterogeneous THC potencies. Similarly, the recent launch of a large and multifaceted longitudinal study of risk modifiers and early-onset substance use [144] should help uncover weak associations or other significant if modest effect sizes.

Cardiovascular Complications

Close to 90 million Americans suffer from at least one cardiovascular condition, like hypertension, stroke, or myocardial infarct. Cardiovascular diseases (CVD) account for nearly 30% of all deaths in the United States [151]. It is true that these forms of morbidity and mortality disproportionately impact older adults [83], who display a relatively low prevalence of current cannabis use (2% for 50 years vs 20% among those 18 to 25 years of age) [7]. However, the high prevalence of these conditions, combined with increasing acceptance, legality, and likely use of cannabis for recreational or medicinal purposes, justifies the hypothesis (and concern) that even a modest mechanistic contribution to increased CVD risk could lead to a significant spike in the number of cases attributable to cannabis use. At the same time, it is worth mentioning that tobacco smoking, which is a well-known risk factor for CVD [73], is highly prevalent among older individuals [70], which makes tobacco a more formidable confounding factor to contend with when investigating any potential cannabis-CVD links.

Over the years, there has been a steady buildup of reports (mostly case reports and small studies) on the effects of acute or chronic cannabis exposure on a long list of cardiovascular, cerebrovascular, and peripheral vascular measures and functions [141]. The preponderance of the evidence appears to support the notion that acute cannabis consumption can cause increased (20–100%) heart rate [14] and blood pressure (more specifically systolic blood pressure) [4, 14], although exceptions to the latter finding can also be found [36]. Inconsistent results could be due to the complex effects of cannabinoids on central vs peripheral circulation. Indeed, cannabis use may impair the circulatory responses to standing, which could help explain the sporadic reports of orthostatic hypotension among some cannabis users [133], likely due to decreased vascular resistance [4]. However, as tolerance develops, both the hyper- and hypotensive effects of cannabis may attenuate over time and eventually disappear [72, 110]. In addition, case studies have also associated cannabis use to increased risk of arrhythmia [35] (including ventricular tachycardia and potentially sudden death); ischemic stroke [141], particularly among healthy young patients [52]; recurrent [129] or acute coronary syndrome with elevated ST segment [49]; and myocardial infarction (MI), immediately or soon after smoking cannabis [24, 37, 94, 100, 142]. Cannabis use has also been reported to be associated with peripheral atherosclerotic disease, sometimes referred to as cannabis arteritis [118, 131], a condition that is indistinguishable from thromboangiitis obliterans (Buerger's disease) [74, 126] that has also been causally linked to tobacco smoking [53].

The mechanisms by which cannabis could affect so many facets of the circulatory system are poorly understood, but given that cannabis contains >500 different compounds, including >100 different cannabinoids [40], they are likely to involve multiple alternative pathways. Indeed, cannabinoid receptors of both types are expressed throughout the tissues that are relevant in this context, including the myocardium, vascular endothelial and smooth muscle cells, circulating blood cells, and the peripheral nervous system (including vagal afferent neurons), where cannabinoid receptors (CBRs) could be activated by endo-, phyto-, and synthetic cannabinoids (reviewed in [114]) and modulate the cardiovascular system.

For example, preclinical studies have shown that acute administration of rimonabant, a CB1R antagonist, can protect against the cardiodepressive effects of doxorubicin (DOX)-induced cardiotoxicity [104] and reduce blood pressure in a rat model of angiotensin II-dependent hypertension [132]. At the physiological level, serious myocardial infarctions (MI) could result from increased myocardial oxygen demand [46, 54, 65, 146] or be triggered by increased parasympathetic activity leading to asystole [18, 97]. In humans, there have been several case reports of cannabis consumption triggering acute coronary syndromes in young individuals, even in the absence of any known common risk factors [39, 49, 82]. While these cases could be classified as anecdotal at this point, they do provide potential insights into more meaningful mechanistic questions to be addressed in larger studies. For example, some authors have suggested that cannabis may promote the generation of reactive oxygen species leading to oxidative stress, a known mechanism of stroke in humans [150].

However, primary and case studies such as these should be taken with a grain of salt, since evaluation of specific vascular effects attributable to cannabis is typically complicated by the presence of other drugs (e.g., alcohol, cocaine) in the system or the concomitant use of tobacco. Still, the temporal association between consumption of herbal mixture products

containing synthetic cannabinoids, such as Spice and K2 [130], and a growing number of reported cases of myocardial ischemia [27] supports the notion that phytocannabinoids may contribute directly to some of the observed effects and warrant further research.

Other Potential Medical Consequences

Reproductive/Endocrine System

There is a bidirectional relationship between the ECS and gonadal hormones, with endocannabinoids downregulating hypothalamic-pituitary-gonadal activity and gonadal hormones modulating protein expression in the ECS and influencing human behavior [51]. The hypothesis that cannabis use could perturb reproductive health hinges on at least three lines of evidence. First, chronic cannabis use may have adverse effects on multiple endocrine systems including prolactin, oxytocin, thyroid hormone and growth hormone [41], and estrogen [88]; second, exogenous cannabinoids could interfere with an endocannabinoid signaling that is operative in all critical stages of pregnancy [92]; and, third, there is preclinical evidence showing that cannabis can impair reproductive function; for example, chronic (36 weeks) THC exposure can cause testicular recrudescence and lower sperm count, viability, and motility in rodents [10]. Despite some evidence in support of these arguments, the notion that cannabis use has a robust adverse effect on male [38] or female [19] fertility in humans remains largely hypothetical. It is possible, as it has been suggested, that the effects of cannabis use on spermatogenesis or testosterone levels may cross the threshold of detection among those whose fertility is already impaired [58], but the fact remains that the results of human research in this context have been inconsistent [21].

Pregnancy Complications

We do know that a carefully calibrated ECS is essential for successful reproduction, a delicate balance that could be disrupted by exogenous cannabinoids [19]. Thus, it is not surprising that, compared with nonusing controls, women who used cannabis during their pregnancy had slightly increased odds of suffering from anemia [55]. In addition, their cannabis exposed infants are more likely to suffer from lower birth weight and to need placement in the neonatal intensive care unit compared with infants whose mothers had not use cannabis during pregnancy [55]. Finally, continued maternal marijuana use at 20 weeks' gestation has been found to be associated with spontaneous preterm births (SPTB), independent of cigarette smoking status [89].

The potential medical consequences of cannabis use in this population are particularly worrisome when we consider that young pregnant women may be turning to cannabis in increasing numbers for its antiemetic properties, particularly during the first trimester of pregnancy, which is the period of greatest risk for the deleterious effects of fetal exposure to drugs [20, 127]. Research and dissemination will play a critical role in counteracting the misleading messaging in multiple media outlets, including the Internet, touting cannabis as a benign solution for the nausea that commonly accompanies pregnancy, including the severe condition known as hyperemesis gravidarum, that could in fact be exacerbated by exogenous cannabinoids [5](see next section). A detailed review of the CUD during the perinatal period is covered in Chap. 14 of this book.

Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS) refers to a clinical entity that used to be rare, under-recognized, or controversial. It was first described in 2004 [3] but has been observed with increased frequency among cannabis users [63, 77, 124]. Affected individuals present to the emergency department with nausea, vomiting, and abdominal pain, a manifestation sometimes referred to as "cyclical vomiting" [119] that is difficult to treat but reported to subside with hot hydrotherapy [125], topical capsaicin in the periumbilical region [102], or stopping cannabis use altogether [17]. Interestingly, a National Academies of Sciences, Engineering, and Medicine (NASEM) report makes no mention of this condition in its latest comprehensive review of the health effects of cannabis and cannabinoids [106], another likely reflection of the fluid nature of this field and the increasing use of cannabis and synthetic cannabinoids. Indeed, more than half of the 145 articles retrieved from PUBMED using the keywords cannabis/marijuana hyperemesis were published just in the past 3 years.

The condition is paradoxical, since THC, the only FDA-approved cannabis-based medication, is prescribed to improve appetite and for the treatment of chemotherapy-induced hyperemesis [42]. It has been hypothesized that CHS may be the manifestation of an endocannabinoid system that, in vulnerable individuals (e.g., deficits in the HPA axis response to stress), becomes unable to withstand the allostatic burden of a high-potency cannabis challenge [124] under conditions of stress or fasting, for example. Although many potential mechanisms have been proposed, including desensitization of CB1R, decreased GI motility, or dilation of splanchnic vasculature (reviewed in [135]), the actual mechanism(s) remains a mystery. Given the rapidly changing cannabis landscape, underdiagnosis of CHS could be on the rise; hence, physicians and healthcare staff should

become more aware of the phenomenon and the standard operating procedures that have been proposed for its diagnosis, treatment, and follow-up [17].

Metabolic Effects

Endocannabinoid research has clearly established the role of these neurotransmitters in the regulation of appetitive behaviors, energy balance, insulin sensitivity, pancreatic β-cell function, and lipid metabolism [80, 90, 115, 149]. Consistent with the metabolic involvement of the ECS, the literature is studded with examples of cannabis adverse effects on multiple related measures. For example, a cross-sectional study found that compared to controls, chronic cannabis smokers reported significantly higher carbohydrate intake and percent calories from carbohydrates (although not total energy intake) and had higher visceral adiposity and lower adipocyte insulin resistance index [105]. While these effects may explain the reported higher odds of displaying signs of prediabetes among young adults who use cannabis [9], recent analysis of all the available data failed to detect increased odds of developing diabetes among regular users of cannabis [9, 134]. In fact, the limited evidence appears to suggest the opposite, namely, that cannabis use and risk of metabolic disease and diabetes might be inversely correlated (reviewed in [106], which is rather unexpected, given THC's ability to increase appetite and promote feeding and fat deposition [140].

Sleep Disorders

There are bidirectional effects between chronic cannabis use and sleep disorders or sleep problems [116]. On one hand, acute or chronic smoking of cannabis is associated with poor sleep quality and inattention [91, 111] and impaired circadian entrainment [147], while CUD is associated with sleep disorders including insomnia [28, 29]. On the other hand, poor sleep or other sleep problems also lead to the development of SUD or CUD among adolescent and young people [6, 62, 98, 99, 107]. Both preclinical and clinical studies have provided evidence that cannabinoids can affect circadian biology and sleep: rodent studies have found significant alterations of circadian rhythm profiles during THC administration [117], while acute THC administration appears to reduce rapid eye movement (REM) but increase slow wave sleep [120] in humans. However, it is likely that the system can develop tolerance to these effects since studies of chronic THC administration have produced opposite or inconsistent results [1, 11, 12, 121]. Interestingly, results of a more recent study of chronic daily cannabis users suggest that higher evening levels of circulating THC or its metabolites may promote shorter sleep latency and facilitate falling asleep [50]. However, a similarly designed experiment suggested that cannabis naïve individuals may be more likely to experience adverse effects after acute exposure to THC, like increased awake activity during sleep time that can counteract any residual sedative property of the drug [108]. Finally, nabilone, a synthetic cannabinoid that mimics THC, may reduce nightmares associated with PTSD and improve sleep among patients with chronic pain [8].

The literature in this area is far from homogeneous and rather inadequate for drawing solid conclusions or crafting clinical guidance. However, the involvement of the ECS in the regulation of circadian physiology is rather clear and may help explain, for example, why sleep disturbances are such a frequent sign of cannabis withdrawal syndrome [28, 47, 48]. Importantly, unlike other cannabis withdrawal symptoms [22] that typically resolve after 2–3 weeks of abstinence (e.g., mood disturbances, gastrointestinal dysregulation), impaired sleep related to CUD may persist up to a month or longer [23, 145], making it a major risk factor for cannabis use relapse among people who are trying to quit or cut down on its use. Thus, clinicians would be well-advised to be on the alert for any sudden changes in sleep hygiene that could be related to acute cannabis exposure or to cannabis withdrawal.

Cancer

After many years of investigating the carcinogenic potential of regular cannabis use, the tide has definitely shifted, in recent years, with a more prominent research focus on cannabis and its emerging (albeit so far unproven) therapeutic role in cancer [71]. As mentioned earlier, smoking cannabis has not been shown to increase the risk of developing lung cancer; however, the data here, and as it pertains to other types of cancer, suffer from the same limitations that bedevil the study of other clinical outcomes. They include small populations, reliance on self-reporting, poor stratification based on cannabis dosages, and a host of confounding and other hard-to-capture risk factors.

Cancer studies present particularly challenging methodological issues, like the targeting of multiple organs, dynamic staging, histopathological heterogeneity, and very long incubation periods. Given the limited quality of the available epidemiological evidence and the likelihood that the prevalence of regular cannabis use will continue to rise, it would be premature to dismiss outright a possible link between cannabis use and cancer. Indeed, there is currently evidence, albeit limited, suggesting chronic or frequent use of cannabis may be associated with testicular germ cell tumors as compared to nonusers of cannabis [56]. Future studies will have

to address the limitations mentioned above and conduct far more rigorous studies vis-á-vis patient stratification and data collection, among others, if we are ever to establish, with a reasonable degree of certainty, whether and which types of cancer risk might be modulated by cannabis use.

Questions Moving Forward

The changing regulatory, scientific, and cultural landscape that influences the prevalence and usage patterns of cannabis requires we adopt a proactive stance vis-á-vis the potential for medical consequences that could affect large numbers of regular users around the globe. This realization translates into an urgent need to identify and address critical gaps in our knowledge, including possible consequences related to:

- *Increasing THC potency*
  There is convincing (although not yet overwhelming) [59, 81] evidence that higher potency strains or extracts of cannabis are becoming widespread and increasingly available, a trend that may be fueled in part by the legalization wave sweeping the nation. For example, a 2014 analysis of Twitter activity showed the highest popularity of dabs (cannabis concentrates reported to reach THC concentration in the 25 to 75% range [122]) was detected in states that allow recreational and/or medicinal cannabis use [31]. This trend is handicapping the ability to derive meaningful lessons from older epidemiological studies that were based on significantly lower THC concentrations [41]. The public health implications associated with high-potency cannabis are not yet clear [81]; thus research in this area, particularly the impact on the developing brain, is urgently needed.

  It is reasonable to expect that users of high-potency products could increase their risk of developing respiratory problems or experience psychotic symptoms [58]. At the same time, we should also consider that experienced users may be able to titrate the dose delivered and effectively lower the risk of health effects, while naïve users may be more likely to experience adverse (or even catastrophic) effects that could deter (or prevent) them from becoming repeat users [58].
- *Overdose, poisoning, and cannabis edibles*
  According to the NASEM, there is "minimal literature on cannabis-related overdose death in adults or children," thus, not enough evidence to support or reject the possibility of a cannabis overdose death. However, pediatric overdose injuries are increasingly a distinct possibility, particularly in states that have legalized cannabis [106]. The US experience with pediatric cannabinoid overdose is consistent with seven cases (between the ages of 1 and 3 years of age) reported over a 3.5-year period in France [86] and another four recorded poisoning cases (between the ages of 2 and 14) in Spain [30]. In general, if cannabis can cause poisoning, it has been in extremely rare occasions up until recently. An analysis of the National Poison Data Systems database involving more than two million human exposure cases in 2012 did not list cannabis among the top causes of death related to pharmaceutical products [32], and prior years only record isolated cases [106]. The Drug Abuse Warning Network reported a significant increase in emergency department visits and rates for cannabis-only and cannabis-polydrug use between 2004 and 2011 [154]. But deaths attributed to the consumption of cannabis containing edibles are beginning to appear in the literature [60], suggesting that increased availability and potency of cannabis products create the potential for an increased risk of adverse health effects related to cannabis use, including overdose, injury, and death. At a minimum, the emerging data strongly suggests that pediatric intensivists should be especially aware and vigilant with regard to the various pediatric symptoms that can be caused by ingestion of cannabinoid-containing products.
- *Medicinal use*
  There is a wide and worrying gap between the strength of the scientific evidence and the intensity of the public's (growing) acceptance of cannabis, cannabis-derived products, and purified cannabinoids for a bewildering array of medical conditions. This warrants a more careful approach to the study of the therapeutic benefit index and potential for specific adverse effects, particularly when dealing with patient subpopulations (e.g., HIV, immunosuppressed, elderly, chronic pain, mentally ill, pregnant women) that are likely to display increased vulnerabilities to iatrogenic harm. A related concern is the almost certainty of the emergence of a robust cannabis retail and advertisement environment, a development that requires a proactive research and surveillance stance [15, 85] in order not to make the same mistakes we continue to make in the domain of legal drugs (i.e., alcohol and tobacco) and other unhealthy (e.g., junk food) behaviors [78].
- *Vaping adolescents*
  One increasingly popular way of self-administrating cannabis is the use of vaporizers or e-cigarettes [103]. Lower temperature vaporization of cannabis has been postulated as safer than smoking, as it may deliver fewer high molecular weight components than smoked cannabis [16], but well-controlled, long-term studies with specific subpopulation will be needed to demonstrate, refute, or qualify this notion. Whether vaporizing cannabis is a safer alternative to smoking remains uncertain, as the reduction in toxic smoke components needs to be weighed against the

hazards of acute intoxication and long-term consequences to the brain due to the formation and delivery of new potentially dangerous compounds, like acetaldehyde and formaldehyde [143]. Of particular concern is the targeted marketing of these highly addictive devices to adolescents, whose developing brains are significantly more likely to experience adverse effects (e.g., addiction, abnormal reward sensitivity) than adults [84, 103].

- *Synthetic cannabinoids*
  Research will be needed to understand the effects of synthetic compounds with different pharmacological profiles and/or higher affinities for cannabinoid receptors [33]. Past studies of THC may not be applicable to explaining new effects seen, for example, on drivers under the influence of synthetic cannabinoids who may be more frequently impaired with confusion, disorientation, and incoherent, slurred speech than drivers under the influence of cannabis, as determined by Drug Recognition Expert (DRE, [61]) evaluation [26]. However, the rise of synthetic cannabinoids presents a constantly changing and particularly evasive threat to public health, which will require more than additional basic research or tighter regulations. A targeted prevention and policy research agenda is needed to identify evidence-based interventions to inform/shape behavioral choices that mitigate the ever-changing risk of adverse health consequences from synthetic cannabinoids [43].

Conclusions

The types of (non-cognitive) medical consequences associated with cannabis use that appear to be supported by a substantial amount of evidence (i.e., strong evidence of a statistical significant link) are few and far between [106]. Most other reported adverse health effects are supported by evidence that is limited in scope or of low quality. Given the rapid changes in cannabis policies and evolution of cannabinomimetic molecules, the large numbers of current users, and the concomitant rise in its medicinal and recreational use, the lack of conclusive evidence, either confirming or rejecting so many of the alleged health effects of cannabis use (whether acute or persistent, adverse or therapeutic), constitutes a grave public health concern. This should spur targeted efforts to (a) design and deploy better surveillance instruments, (b) conduct more basic cannabis research in animals and humans, and (c) develop a prevention research and policy agenda that can address the many complex issues associated with today's patterns of cannabis use.

Disclaimer *The opinions in this paper are of authors and do not reflect the position of the National Institute on Drug Abuse, National Institutes of Health.*

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Synthetic Cannabinoid Use

16

Laurent Karila and Amine Benyamina

Introduction

New psychoactive substances (NPSs) provide users with alternatives to older and better-characterized drugs of abuse, such as cocaine, MDMA or cannabis. The endocannabinoid system is known to have an effect in regulating appetite, nausea, mood, pain or inflammation [1]. In 1990, a research group mapped the location of cannabinoid receptors in the human brain (cannabinoid receptor type 1 or CB_{1R}). In 1993 peripheral cannabinoid receptors (cannabinoid receptor type 2 or CB_{2R}) were cloned [2].

Initially developed in Europe and in the USA as ligands to study the endocannabinoid system, synthetic cannabinoids (SCs) share no structural commonality with the Δ9-tetrahydrocannabinol (Δ9-THC or THC), which is the substance that is primarily responsible for the main psychoactive effects of cannabis. In contrast to Δ9-THC, SCs have been shown to act as full CB_{1R} and CB_{2R} agonists in both cellular assays and animal studies [3]. There are six main chemical classes of exogenous cannabinoid ligands that differ in structure, lipophilicity, and binding activity in cannabinoid receptors (Table 16.1) [4, 5] (see Reference 16.1).

Known as *Spice* [6] in Europe or *K2* in the USA, these products contain non-psychoactive plant material. SC compounds are mixed with plant products on an industrial scale using solvents (e.g. acetone, methanol) to dissolve the powders which exert psychoactive effects when smoked. Their composition in terms of synthetic additives and/or substances is changing fast and rapidly responding to the new European control and regulation efforts [7]. SCs also take the form of tablets, capsules, powders [8] or new liquid products to be used in electronic cigarettes [9].

Developed in laboratories in China and South Asia [10], SCs have been available in several European countries (Germany, the UK, Switzerland) since 2004 [11]. However, it was not until 2008 that forensic investigators in Germany and Austria identified the first psychoactive constituent of Spice products, the JWH-018 aminoalkylindole [12, 13]. In 2009, the "Spice phenomenon" received considerable attention in the mass media, among politicians and in the scientific community [14, 15]. Besides the chemical names derived from the initials of the scientists who first synthesized them [11] (JWH [16], AM, CP or "HU" compounds [14]), SCs are now given code names that are derived from their full chemical names (APICA, APINACA, MDMB-FUBINACA, MDMB-CHMICA, etc.).

Substantial variations can occur in content and concentration of SC compounds in many available products, even within the same brand or batch [14, 17–19]. These new synthetic drugs are mainly sold online (*darknet*) as an alternative to controlled and regulated psychoactive substances [20, 21]. SCs are also available in some countries through head shops or smart shops selling accessories for smoking cannabis. They are also distributed by street drug dealers and organized-crime groups as inexpensive alternatives to traditional drugs of abuse. SCs are shipped as bulk powders to Europe using express mail and courier companies. Larger amounts can be shipped by sea cargo or air. Each kilogram of bulk powder can produce thousands of packets of SC. There is also evidence of a significant Internet retail trade within Europe and the USA. SCs play an important role in the rapidly evolving "legal high" market [11].

In terms of public health, there is incentive to improve current approaches to monitoring, responding to and controlling SC use [22]. The main available information on SCs can be obtained through the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA), the European Union Early Warning System (EU-EWS) reports, the National

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Table 16.1 Classification of synthetic cannabinoids

Classical cannabinoids	Nonclassical cannabinoids	Hybrid cannabinoids	Aminoalkylindoles
HU-210, AM-906, AM-411, O-1184	Cyclohexylphenols or 3-arylcyclohexanols such as CP-47,497-C8, CP-55,940, CP-55,244	Combinations of structural features of classical and nonclassical cannabinoids, e.g. AM-4030	Naphthoylindoles (e.g. JWH-018, JWH-073, JWH-398, JWH-015, JWH-122, JWH-210, JWH-081, JWH-200, WIN-55,212); phenylacetylindoles (e.g. JWH-250, JWH-251); naphthylmethylindoles and benzoylindoles (e.g. pravadoline, AM-694, RSC-4)

Eicosanoids	Others
Anandamide Other synthetic analogues, e.g. methanandamide	Diarylpyrazoles (selective CB_1 antagonist) Naphthoylpyrroles (JWH-307), naphthylmethylindenes or derivatives of naphthalene

Reitox reports, the US *Monitoring the Future* study, the Drug Abuse Warning Network, the Internet underground, several governmental websites and specialized discussion groups and forums [23].

The aim of the current chapter is to review the available data regarding the effects and consequences of SC use in humans. A literature search was performed on two representative databases, PubMed and Science Direct, and various websites mentioned above. The terms used for the database search were "synthetic cannabinoids", "spice", "K2", "synthetic cannabis", "legal highs", "new psychoactive substances", "harmful use", "adverse effects" and "fatalities". The search was limited to the years 2005 to 2017. The literature search led to the identification of 122 potentially relevant articles. All articles were screened from their abstracts to determine their relevance in the framework of the current review.

Epidemiological Data

SCs are the largest group of substances currently monitored by the EU-EWS. A total of 169 SCs have been notified to the EMCDDA since December 2016 (one in 2008, 9 in 2009, 11 in 2010, 23 in 2011, 30 in 2012, 29 in 2013, 30 in 2014, 25 in 2015 and 11 in 2016).

SCs are becoming increasingly popular among adolescents as a substance of abuse [24]. Students and clubbers are, for the most part, experienced cannabis users, buying these substances on the Internet [7, 25]. According to the 2017 EMCDDA report, the prevalence of SCs in the general population remains low. In a worldwide survey of 14,966 participants, 17% reported SC use [26].

There are differences between the prevalence of SC use between Europe and the USA. According to the Drug Abuse Warning Network (2012), 11,406 hospital emergencies were associated with SCs in 2010: 75% were among adolescents and young adults (12–29 years old); 22.5% of these emergencies involved females, and 77.5% involved males. In 2012, the US *Monitoring the Future* survey of students showed that SCs were the second most widely used drugs after cannabis, with a past-year prevalence of 11.4%. A past-year prevalence of SC use among 17–18-year-olds of 5.8% was reported in 2014 [27].

Data from the two most recent cohorts (2014–2015; N = 7805) reported the prevalence of self-reported use. Differences in demographics and frequency of use of other drugs were compared between current marijuana-only users and current SC (plus marijuana) users. It was found that 2.9% of students reported current SC use and 1.4% of students (49.7% of users) reported using SCs on 3 days or more in the past month. SC users were more likely to report more recent (and often more frequent) use of cocaine, heroin and/or nonmedical use of opioids compared to marijuana-only users [28]. According to the National Institute of Drug Abuse survey on 8th, 10th and 12th grades, 3.1%, 4.3% and 5.3% were identified as using synthetic SCs in 2015 [29]. In a field-based study in New York City nightclubs, 8.2% of the 1749 adults reported having used SCs in the past year [26].

A number of epidemiological surveys have examined the prevalence of SC use in Europe [7]. The UK reported lifetime prevalence levels of Spice use for adults of 0.2% in 2010/2011 [30] and 0.1% in 2011/2012 [31]. Among UK regular clubbers, the 2012 Global Drug Survey reported past-year prevalence levels of 5% [32]. A lifetime use of herbal mixtures of 5% was found among students aged 15 to 18 years in Germany in 2013 [33]. In France, an experimentation level of 1.7% was found among 18- to 64-year-old adults in 2014. First-time users are mostly men (2.3%), and 4% of them are aged under 35 [34]. A French survey, the ESCAPAD project, highlighted that 1.7% of people aged 17 years old had already consumed SCs [35]. Low-level use of Spice products were described among students aged 14 to 18 in Spain in 2012 with a lifetime use of 1.4%, a past-year use of 1% and a past-month use of 0.6% [36]. Among current marijuana and tobacco users in the USA, SC use is

common and persists despite a federal ban. The primary reasons for the use of SC-containing products seem to be attempts to evade drug detection and experience cannabis-like highs [37].

Clinical Effects

SCs have many commercial and street names (see Table 16.2). They do not contain tobacco or cannabis [38]. Clinical effects of SCs, as with other NPSs, depend on the individual, the dose and the route of administration [39]. Effects begin only a few minutes after inhalation and generally disappear after approximately 2–8 hours. SCs reportedly have both a shorter duration of action and a quicker time to peak onset of effect [20]. Orally ingested SCs are likely to have a slower onset of action (and less intense effects) but a longer duration of effect than inhaled products [26].

The majority of their psychoactive effects are comparable to those of Δ^9-THC: euphoria, well-being, sedation, lethargy, facilitated laughter, talkativeness, disinhibition [13], intensification of sensorial experiences, perceptual distortions and social withdrawal, conjunctival hyperaemia, increased appetite, dry mouth, increased blood pressure, tachycardia (heart rate increases by 20–50% within a few minutes to 25 minutes) [14] and acute bronchodilation effects [40]. Sensory changes; visual, tactile, and auditory perceptions; perceptual illusions; hallucinations; and a feeling of distorted time perception have been described [40]. In a laboratory study, 10 minutes after smoking a cigarette of Spice Diamond, Auwarter et al. found altered mood and perception, moderately impaired psychomotor activity, tachycardia, dry mouth and red or bloodshot eyes. Objective effects were resolved after 6 hours. Noticeable minor after-effects were reported the next day [41].

Table 16.2 Examples of street names of synthetic cannabinoids

Albino Rhino Buds; Aroma
Black Mamba; Bombay Blue
Crazy Clown, Caneff 5 star; Chillin XXX
D-Raw; Dark Matter
Everlast; Experience: Chill; Experience: Ignite; Experience: Red Ball
Fake marijuana; Fake Weed; Flare Space
Galaxy; Genie; Gorilla
Herb Dream; Herbal incense
Ice Bud Extra
K2; K3; K3 Legal; Kronic
Magic Mojo; Moon Rocks
Pep Spice
Red Magic Sence Skunk
Smoke Solar; Spice; Spice Arctic; Synergy Spice Tropical; Synergy Spice Diamond;
Spice Gold; Spice Gold Spirit; Spice Silver; Spicey XXX; SpiceWorld420; Spice99;
Spike99; Smoke Splice Platinum
Yucatan Fire
Zohai; Zohai SX

Adverse Outcomes Associated with the Use of SCs

Distinct pharmacological properties and metabolism of SCs relative to Δ^9-THC may contribute to the observed toxicity [3, 42]. Early evidence suggests that adverse outcomes associated with the use of SCs may be more prevalent and more severe than those arising from cannabis use [43].

Somatic Adverse Effects

Physical Signs

Physical signs of acute SC intoxication are nausea, vomiting, slurred speech, sweating or skin pallor, dilated pupils, reddened conjunctivae, shortness of breath, physical instability and muscle twitches [44–46].

Cardiovascular Effects

Tachycardia [47], less frequently bradycardia [48], tachyarrhythmia [49], QTc prolongation and torsades de pointes (TdP) [50], hypertension [51] and hypotension [52], chest pain and myocardial infarction [53] have been reported. SC use should be included in the differential diagnosis of young patients with no risk factors presenting with venous or arterial thrombosis [54].

Neurological Effects

Neurological effects including fasciculations, hypertonicity, hyperflexion/hyperextension, tremor, ataxia, nystagmus, drowsiness, dilated pupils, involuntary eye movement, slow speech, agitation, and impaired memory have been reported [40, 55]. Serious central nervous system effects include confusion [56]. After vaporizing SCs, MRI imaging has demonstrated restricted diffusion and increased T2/FLAIR signal in the corpus callosum and cerebellar peduncles of a woman [57]. Haemorrhagic [58] and ischemic stroke [59], emboli [43, 60–62] and generalized tonic-clonic seizures have also been described [40]. A case of SCs revealing adrenoleukodystrophy has been reported. The authors hypothesize that cannabinoid use might have contributed to metabolic decompensation with subacute worsening of the underlying condition [63]. SCs can lead to impairments similar to typical performance and cognitive deficits caused by cannabis use [64].

Gastrointestinal Effects

A case of cannabinoid hyperemesis syndrome [64] involving a heavy chronic user of synthetic cannabinoids (JWH-018, JWH-073, JWH-122, AM-2201 and AM-694) has been described [65]. The first known case of synthetic cannabinoid hyperemesis leading to rhabdomyolysis and acute renal failure was reported by Argfamany et al. [66]. A very rare case of acute gastric dilatation (AGD) and hepatic portal venous gas (HPVG), with acute abdomen resulting from chronic use of a SC, Bonzai, has been described [67]. A few cases of SC ingestion have also been associated with liver failure [68].

Nephrotoxic Effects

Nephrotoxic effects have risen with the increasing frequency of SC use [69]. Kidneys can be damaged in diverse ways by SC use [70]. Acute kidney damage [43], related to XLR-11 [71] and other SC use [72–74], and rhabdomyolysis, which may be a mechanism in acute kidney damage, have been reported [75–77]. Effects reported include vomiting, flank pain, abdominal pain, urinary and serum creatinine elevation (3–21 mg/dL) with proteinuria and haematuria in some people [43, 72].

Metabolic Effects

Adverse effects linked to ADB-PINACA including hyperglycaemia and hypokalaemia among other symptoms have been reported in 22 patients admitted to emergency unit in Brunswick, Georgia [78].

Pulmonary Effects

Pulmonary damage from SC use can result from butane incineration. If not completely removed, it explodes during incineration and may cause pneumothorax and pneumomediastinum [43, 79]. Diffuse pulmonary infiltrates have been found [80, 81]. Pneumonia has been described in the context of ADB-PINACA use [82]. A case of SC as a potential cause of black carbonaceous bronchoalveolar lavage was reported [83].

Dermatological Effects

The most frequent dermatologic complaints among SC users are periorbital darkening, hollowed cheeks and premature ageing, hair loss and grey hair and acne. The most frequent dermatological examination findings are artefact lesions such as blade scars, tattoos and acne [84]. Oedema (0.2%), erythema (redness of skin) (0.2%), hives (0.2%), irritation/pain (0.4%), pallor (1.3%), itchy skin (0.2%) and rash (0.2%) have all been reported [40].

Psychiatric Adverse Effects

Psychiatric presentations include agitation, depressed mood, hyperactivity (SC-induced mania) [85], insomnia, anxiety, panic attack, paranoia [43, 44, 86], flashbacks [87], cognitive impairments and self-mutilation[88]/self-harm/suicidal ideation [89]. Catatonia, in two patients with no previous psychosis, has been reported [90]. There have been an increasing number of case reports linking SC use to psychosis.

These drugs may have a higher psychosis-inducing potential than cannabis for many reasons. They do not contain cannabidiol [91] and have a more potent effect because of the full CB_1 receptor agonism, compared to THC, which is only a partial agonist. Symptoms such as delirium [92], paranoid delusion, musical auditory or visual hallucinations, disorganized thought and behaviour, irrelevant speech, depersonalization and dissociative episodes have been described [93]. SCs may either exacerbate previously stable psychotic symptoms (in vulnerable individuals) or trigger new-onset psychosis (in individuals with no previous history of psychosis) [94].

Addictive Potential

The addictive potential of SC products is not negligible [21, 95, 96]. Withdrawal symptoms resulting from long-term SC use have been described in the medical literature [38, 51, 97]. Individuals withdrawing from synthetic cannabinoids were the third largest group of patients admitted to inpatient detoxification services in Auckland, New Zealand, between May 2013 and May 2014 [98]. The most commonly reported withdrawal symptoms included agitation, irritability, anxiety and mood swings. Disturbed sleep and dreaming, craving, nausea, muscle twitching or cramp and chills have been found [99]. Withdrawal symptoms can be measured using the Cannabis Withdrawal Assessment Scale (CWAS). In one study, diazepam (5–25 mg daily) was the first inpatient prescribed medication for 4.0 ± 1.9 days. Quetiapine (25–475 mg) was used (duration of therapy: 8.0 ± 3.8 days) only if diazepam was ineffective (MacFarlane et al., 2015). A severe withdrawal syndrome with Spice Gold, including increased craving, restlessness, nightmares, tachycardia (maximum heart rate 125 bpm) and hypertension (180/90 mmHg), has been reported. The syndrome resolved within 1 week with symptomatic treatment [100]. Other researchers found headache, cramps in the extremities, sweats and chills, severe anxiety, vivid dreams, anorexia and craving 1 week after the last use [101].

Outbreaks of Unexpected and/or Severe Toxicity

Several outbreaks of unexpected, severe toxicity linked to SC use have been reported since 2012. In one report, males in general, and those over the age of 30 years, were more likely to experience death or severe adverse events than their female or younger counterparts [102].

For the period August 21 to September 19, 2013, a similar outbreak of altered mental status, tachycardia followed by bradycardia and seizures in 76 patients who presented to the emergency units at two teaching hospitals was reported in Denver and Aurora, implicating ADB-PINACA and brands of SC-containing products [103].

Between May 28, 2014 and June 8, 2014, 35 patients were evaluated and treated at the University of Florida Medical Health Center in Gainesville following reported exposure to AB-CHMINACA, a SC-containing product obtained from a common source. Patients exhibited acute delirium (24) and seizures (14), and 5 required ventilator support and care in intensive care unit [92]. In 2014, in Russia, MDMB-FUBINACA was linked to more than 600 poisonings, including 15 deaths, over a 2-week period [11].

Schwartz et al. reported seven patients who experienced anxiety, delirium, psychosis and aggressive behaviours after smoking the same SC, ADB-PINACA (Crazy Clown), at a party. Another patient presented with delayed-onset seizures [104]. One of the largest outbreaks of SC-associated adverse events ever recorded was in Mississippi. The authors reported that 721 suspected cases of synthetic cannabinoid-induced adverse events were seen on April 2–3, 2015. The main symptoms were tachycardia, elevated systolic blood pressure, aggressive or violent behaviour, confusion and depressed mental state (somnolence or unresponsiveness) [105].

From July 15, 2015 to March 15, 2016, a total of 1351 ambulance transports to Anchorage emergency units for adverse SC reactions were identified. Tests on 25 product and paraphernalia samples collected from patients at 1 hospital identified 11 different SCs [106]. One case series described 11 patients exposed to the synthetic cannabinoid, MAB-CHMINACA who presented to an emergency unit with life-threatening toxicity including severe agitation, seizures and death. All patients required sedatives for agitation, nine required endotracheal intubation, three experienced seizures and one developed hyperthermia. One developed anoxic brain injury and rhabdomyolysis and died [107].

AMB-FUBINACA, also known as MMB-FUBINACA or FUB-AMB, caused a mass intoxication of 33 people in a New York City district. It was described as a "zombie" outbreak because of the intoxicated people's appearance [108]. Strong depressant effects accounting for this "zombie-like" behaviour were reported in this intoxication.

Deaths

SC use should be considered as a potential cause of death [109]. In 2013, four deaths associated with 5F-PB-22 use were reported in the USA [110]. A fatal intoxication was described in relation to ADB-PINACA use in 2014 [111]. Sudden cardiac deaths following the use of MDMB-CHMICA [112] and also with K2 abuse [113] and other SCs [114] have been reported. MDMB-CHMICA in combination with alcohol was involved in a fatal intoxication [115]. Shanks et al. reported deaths related to use of XLR-11 [116], ADB-FUBINACA [117] and 5F-AMB [118]. In July 2016, 28 deaths associated with MDMB-CHMICA were reported to the EMCDDA. As previously seen, deaths can also occur during outbreaks of mass poisoning.

Current Legal Status

The number of SCs and their potential new analogues [119], their chemical diversity and their spread throughout the world make these new synthetic products particularly challenging in terms of detection, monitoring and response. SCs appear to have a short life cycle before being replaced by a new wave of products [120]. Approaches to the scheduling of SCs in the USA include adding specific compounds, scheduling SCs according to their chemical class or family and reference to state and federal analogue acts. Twenty-five SCs have been banned since 2012. In July 2016, 2 senators proposed legislation to add 22 additional SCs to that list after an outbreak of adverse effects that occurred in a single week in New York. The Drug Enforcement Administration (DEA) considered the following drugs to be Schedule I narcotics with no medical value: 5F-ADB, 5F-AMB, 5F-APINACA, ADB-FUBINACA, MDMB-FUBINACA, MDMB-CHMICA and MDMB-FUBINACA. These chemicals rejoin several others that the DEA has rescheduled over the years using the same mechanism.

An extension of the temporary placement of PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA in Schedule I of the Controlled Substances Act has been carried out [121].

In many European countries, a legal status exists for some synthetic cannabinoids.

The legislation regularly changes, with an increasing number of countries classifying them as illegal drugs in an attempt to limit the spread of existing drugs, to restrict their use, to monitor the potential release of new analogues and to adopt a generic classification in contexts where this is possible [96].

In the UK, the Advisory Council on the Misuse of Drugs proposed generic definitions for five SCs. In 2009, five substances were listed by name (HU-210, HU-243, CP 50, 5561, nabilone, WIN-55,212–2) [40]. Four years later, three new generic definitions were added, and some compounds were listed as Class B, Schedule I drugs [40].

Conclusion

Synthetic cannabinoid receptor agonists are a group of substances that mimic the effects of THC. They play an important role in the rapidly evolving *legal highs* market. There are notable differences in the prevalence of use of synthetic cannabinoid products between the European and the US drug markets. Despite increasing worldwide legal restrictions, SCs are widely available via the Internet. Users are exposed to drugs that are extremely variable in composition and potency. SCs may have side effects that are more severe than those of cannabis. Important health-related issues have emerged in relation to the somatic, psychiatric and addictive consequences of their use. Outbreaks of unexpected and/or severe toxicity and related deaths have been reported. Further studies are required to improve prevention interventions and policies, first-line management and psychotherapeutic treatment of individuals displaying SC intoxication or addictive use.

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Cannabis Use Disorder During the Perinatal Period

17

Martha L. Velez, Chloe J. Jordan, and Lauren M. Jansson

Introduction

Cannabis use in the perinatal period has been increasing in recent years, coincident with increasing legalization in the USA for medical or recreational purposes [1]. Marijuana is the most commonly used illicit drug during pregnancy [2], and among some populations, it is used more frequently than tobacco [3, 4]. Although the prevalence of cannabis use during pregnancy is difficult to ascertain with accuracy, rates of marijuana use range from 2.6% to 28% or higher [3, 5] depending on the population studied and/or screening practices. According to the 2013 National Survey on Drug Use and Health, the rate of marijuana and hashish use among pregnant women in the USA was 5.2% [6].

Marijuana use is more prevalent among nonpregnant than pregnant women of child-bearing age in the general population. However, among past-year users, near daily use rates are higher in pregnant versus nonpregnant women (16.2% versus 12.8%), as is the percentages of women meeting criteria for cannabis abuse and dependence (18.1% versus 11.4%) [7]. These statistics indicate that for the population of women using marijuana during pregnancy, many are chronic users who are likely to have a cannabis use disorder (CUD). Young adolescents (ages 15–17) have the highest rate of marijuana use during pregnancy (16.5%), more than double the rate for 18- to 25-year-olds (7.5%) [6, 8]. During pregnancy, rates of marijuana use are higher during the first trimester than the second or third trimester (6.44% vs. 3.34% and 1.82%, respectively) [9]. Given that the percentage of unplanned pregnancies is very high (almost half of pregnancies in the general population and higher in substance using/abusing populations), many fetuses are likely to be exposed to cannabis during the first trimester of pregnancy, before the mother is aware of being pregnant.

The effects of cannabis mainly depend on its major psychoactive cannabinoid (delta-9-tetrahydrocannabinol or THC) content. Novel ways of cultivating the *Cannabis sativa* plant have produced more potent varieties of cannabis [10], and the legal cannabis market has implemented selective growing methods to boost psychoactive potency. In the USA, the potency of cannabis has increased steadily over the past 50 years [11], and this trend has translated to increased fetal THC exposure. For example, tetrahydrocannabinolic acid concentrations were significantly increased in marijuana-positive meconium samples originating from Colorado hospitals compared with specimens sent from the rest of the USA during the first 9 months post legalization in Colorado [12]. The proportion of THC in the commonly used herbal cannabis (marijuana) and its resin (hashish) was 3% or less in the 1960s but reached a potency of 12% by 2014 [10, 13]. This means that marijuana today is at least 4 times more potent than it was 4 decades ago [14], which has implications for the interpretation of older studies on the effects of prenatal marijuana exposure on child development that form the large bulk of our current knowledge.

The emergence on the drug market of synthetics cannabinoids (SCBs) in the early 2000s represents a new public health challenge. Whereas THC generally acts as a partial cannabinoid receptor agonist, SBCs are often full cannabinoid receptor agonists and can have greater cellular actions and behavioral effects. The concentrations of SCBs can vary widely, even within batches of the same product [15]. Some SCBs have extremely high potency, ranging from 40- to 660-fold higher than Δ9-THC in cannabis strains [16]. SCBs are cheap and easily purchased on the Internet, potent, and addictive and possess different toxicity profiles from naturally grown marijuana [17]. These substances appear to produce multiple dose-dependent congenital anomalies in

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rodents [18], and there is no current information on the effects of SCBs in exposed human fetuses or infants.

Despite its controversial nature, the use of medical marijuana and cannabis-derived medicinal products is also becoming more popular in the USA. Nausea, a common complaint in pregnant women, is a medically approved indication for marijuana in all states where medical use of this drug has been legalized [19]. A study carried out in Hawaii, a state where marijuana is legal, found that women with severe nausea during pregnancy, compared with other pregnant women, were significantly more likely to use marijuana (3.7% vs 2.3%, respectively) [20].

Taking this information together, the current landscape of the risks of marijuana use during the perinatal period is not clear because of the recent changes in the patterns of marijuana use, the increase in prevalence of cannabis use in women during the perinatal period, the production and use of more potent forms of cannabis, and the introduction of synthetic cannabinoids. It is well-established that THC crosses the placental barrier, and while a preponderance of studies have established harmful effects of prenatal cannabinoid exposure in animal (e.g., rodent) models, further research is urgently needed to determine the effects of the increased fetal THC exposure.

Prenatal Cannabis Exposures: Impact on the Pregnancy and the Fetus

Cannabis has more than 540 constituents [10]. The plant's behavioral and psychotropic effects are attributed to the major psychoactive cannabinoid, THC. THC has a lipophilic nature and, when inhaled rapidly, enters the bloodstream resulting in swift distribution from the blood to the tissue. In both animals and humans, THC crosses the placenta and transfers to the fetus; however, there is a lack of complete understanding of the pharmacokinetics and maternal-fetal transfer and disposition of THC and its metabolites [21]. Animal studies indicate great variability in THC distribution to fetal tissues across species, although THC concentrations in the fetus have been documented to be lower than maternal concentrations in those animal studies [21, 22]. In studies done in humans when the mother smoked marijuana daily during the third trimester of pregnancy, THC levels in maternal blood were 2.5 to 6 times greater than in cord blood [23].

Biological (Fig. 17.1) and neurodevelopmental/neurobehavioral (Fig. 17.2) effects of prenatal THC exposure have been described across the life span of the developing organism. There are several mechanisms by which THC exposure

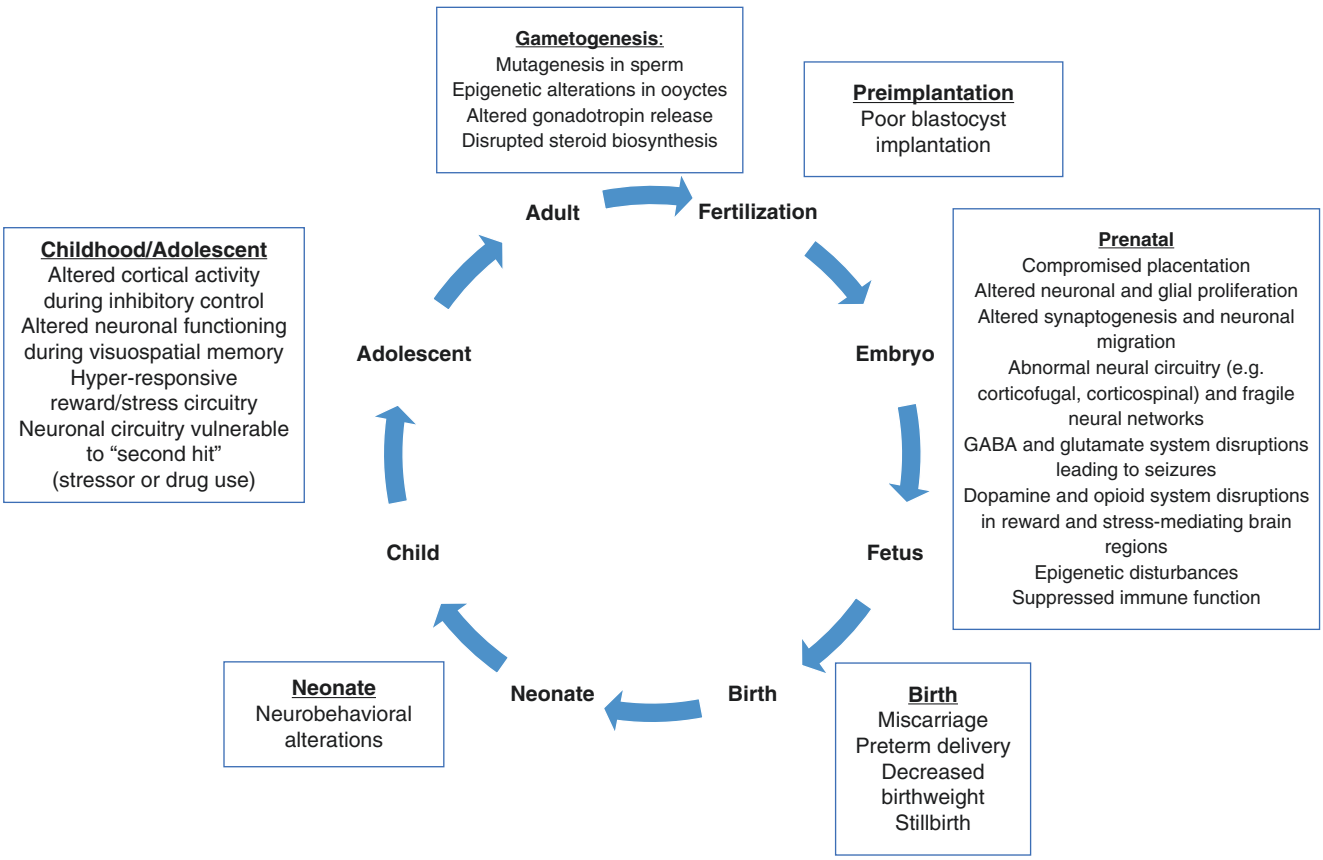

Fig. 17.1 Reported biological disruptions due to prenatal cannabinoid exposure across the human and/or animal life span

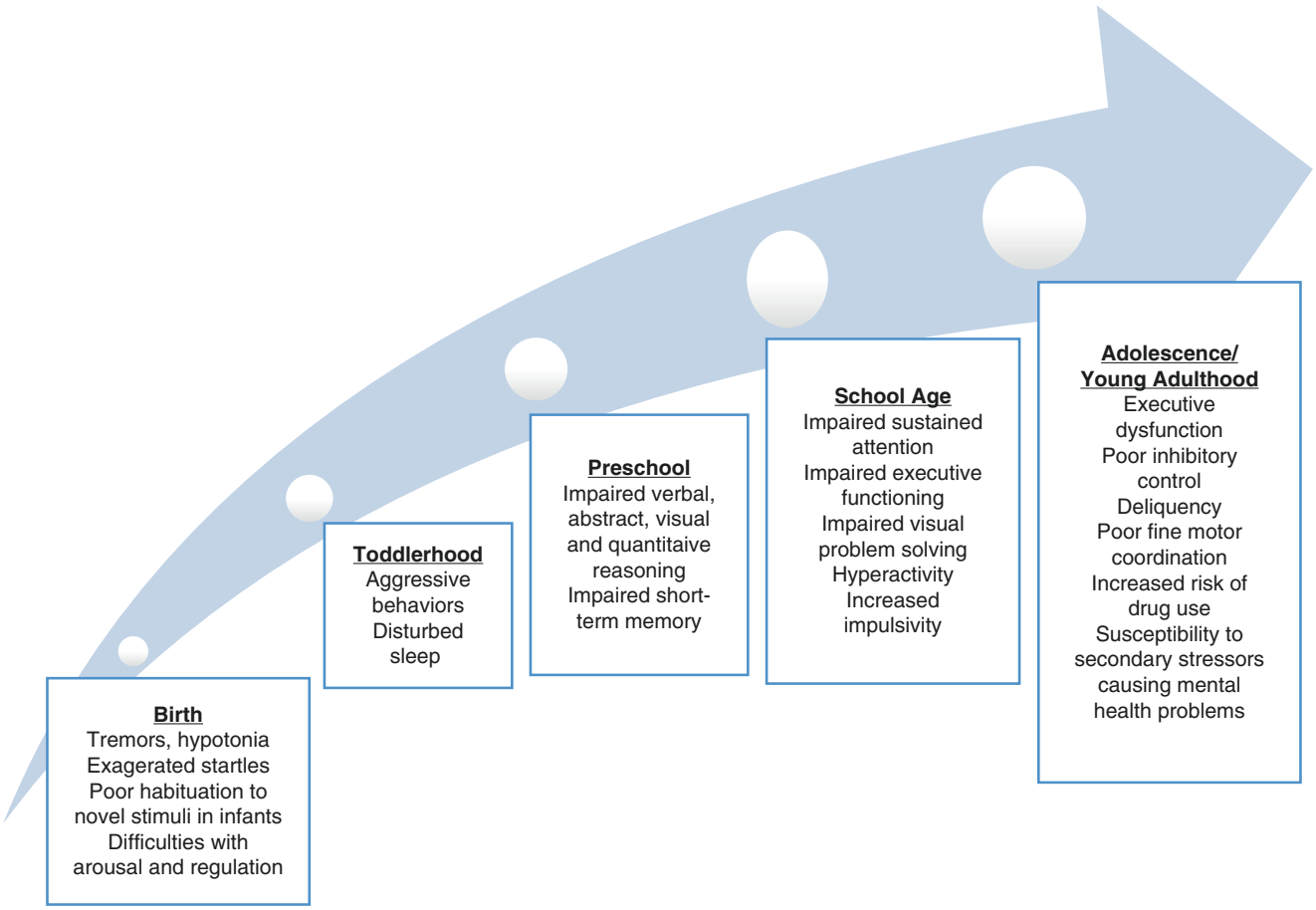

Fig. 17.2 Reported neurobehavioral effects of prenatal cannabinoid exposure across the developmental life span of the child

causes developmental harm in children, including effects of cannabis on the developing endocannabinoid system, effects on neurotransmitters and neural circuit connectivity, and persistent epigenetic modifications which may alter gene expression across the life span.

Mechanisms of Harm

Effects of Prenatal THC Exposure on the Fetal Endocannabinoid System

The endocannabinoid (EC) system describes the body's endogenous or naturally produced cannabinoid system and includes the endocannabinoid retrograde neurotransmitters, their receptors, and the enzymes involved in their synthesis and degradation. The EC system has been detected from the earliest embryonic stage and throughout pre- and postnatal development [24, 25]. Data from both animal and human research indicate that EC system signaling plays a critical role in pregnancy outcome and fetal development. The EC system undergoes significant changes in expression and activity of its components during sequential developmental stages, suggesting ECs play a major role in the formation of specific anatomical regions at timepoints in pregnancy. A fine-tuned orchestration of this system during brain development is essential.

The EC system works both in the central nervous system and peripherally to regulate a myriad of vital functions. Endocannabinoids and plant-derived cannabinoids exert their effects by activating predominantly cannabinoid (CB) receptors. In the fetal nervous system of animals and humans, CB receptor distribution is different from that in the adult, suggesting that endogenous and exogenous cannabinoids may have different effects prenatally than in a mature organism. Expression of CB1 receptors has been detected in the fetal human brain as early as 14 weeks of gestation and changes dynamically across development in different parts of the brain [26] indicating critical roles in orchestrating fetal brain development. In developing fetal human brains not exposed to cannabis, the distribution of CB1 receptor mRNA at approximately 20 weeks of gestation is elevated in limbic structures (including the hippocampal CA region and basal nuclear group of the amygdaloid complex) compared to the rest of the brain. High CB1 receptor concentrations are also present on several white matter neuronal tracts of the human

fetus but had disappeared by infancy [27]. Thus, differences in localization of CB1 receptor expression seem to be a transitory phenomenon, with progressive increases occurring from the fetal period through adulthood. In the adult human brain, CB1 mRNA expression is relatively widespread and is particularly apparent in the frontal cortex, hippocampus, basal ganglia, and cerebellum [27, 28]. Together these findings suggest that CB1 receptors have unique and changing roles in regulating pre- and postnatal development that significantly differ from adulthood.

The two main ECs are N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). They are produced on demand, and their levels are tightly regulated by enzymes involved in their synthesis and degradation. Brain AEA levels are low at midgestation but gradually increase during postnatal development, reaching a maximum in adulthood. In contrast, brain 2-AG synthesis gradually increases during embryonic development, peaks immediately after birth, and normalizes during postnatal development [29]. Prenatally, EC signaling plays a critical role in stimulating the proliferation of progenitor cells, differentiation of these cells toward both glia and neurons, and myelinogenesis. EC signaling also appears to regulate neural cell migration and is involved in the control of axon elongation and guidance, the establishment of synaptic communication, and the acquisition of specific neurotransmitter phenotypes [30–32].

EC (particularly 2-AG) signaling has mechanistically been implicated in the differentiation of dopaminergic and basal forebrain (cholinergic) and cortical (glutamatergic and GABAergic), cerebellar (GABAergic), and hypothalamic (orexinergic) neurons during late gestational and early-postnatal periods in rodents. Therefore, ECs are important neuromodulators of multiple central neurotransmitter systems that are essential for normal fetal brain development. Studies also indicate that a cross talk between the ECs and other neurotransmitters (acetylcholine, dopamine, and serotonin) is essential for proper embryo development.

In addition to the EC system's role in central nervous system development, other systems (e.g., immune and reproductive systems) also have cannabinoid receptors and produce endocannabinoids which could be altered by prenatal exposure to exogenous cannabinoids (e.g., cannabis or SCB consumption) [33–37]. In rodents, the CB1R is present and functionally active in the preimplantation embryo and in the uterus [38]. ECs modulate several reproductive events from gonadotropin release and sex steroid production to the formation of quality gametes and successful pregnancy. Thus, ECs influence reproductive processes from gametogenesis to fertilization and from embryo implantation to the final outcome of pregnancy. Normal physiological EC levels appear necessary in order to achieve optimal neurophysiological outcomes. It is known, for example, that in order to guarantee a receptive uterine environment, AEA levels must be kept low, and this is attained through a tight regulation mediated by N-acyl-phosphatidylethanolamine-specific phospholipase (NAPE-PLD), the enzyme responsible for AEA synthesis, and fatty acid amide hydrolase (FAAH), in charge of AEA degradation. Significant changes in AEA levels have been detected at the end of pregnancy in maternal blood, suggesting that the endocannabinoid system could modulate physiological functions during pregnancy and labor.

Because pre- and postnatal development is critically regulated by the EC system, there are concerns among clinicians and researchers that disturbing the delicate balance of ECs due to exogenous cannabinoids, such as through parental marijuana or SCB use, could negatively impact reproductive potential and fetal brain growth as well as structural and functional neurodevelopment [9]. Disruptions of the EC system by cannabis use may have many negative consequences for pregnancy outcome, including delayed embryo development, poor blastocyst implantation, miscarriage, and altered placenta formation [39].

An understanding of the molecular pathophysiological events that underlie the alterations in embryonic/fetal development related to cannabis prenatal exposure is just unfolding [40, 41]. However, animal and human studies suggest that perinatal cannabis exposure may disrupt the precise temporal and spatial control of EC signaling at critical stages of neural development, leading to negative effects on later nervous system functioning [42].

Prenatal THC Exposure and Effects on Neurotransmitters

Prenatal exposure to exogenous cannabinoids can modify the maturation of neurotransmitter systems and their related functions through the activation of CB1 receptors that emerge early in the developing brain. Animal studies have revealed alterations of neurotransmitter systems associated with behavioral changes relevant to the human condition after administration of cannabinoids, at doses similar to those found in cannabis users. For example, THC binding to CB1R during gestation alters development of central dopamine and opioid neurotransmitter systems in brain areas regulating reward and motivation, which may increase vulnerability to future drug use and addiction in later life [43, 44]. In addition to evidence from animal studies, postmortem examination of human fetal brains with prenatal cannabis or THC exposure reveals reduced dopamine D2 receptor mRNA in the basal nuclear complex of the amygdala, accompanied by a lesser reduction in the nucleus accumbens. Reduced D2 receptor mRNA was correlated with the amount of maternal marijuana intake and was more prominent in males [43]. This gender-specific imbalance in dopaminergic development might

explain why boys exhibit greater deficits in attention, learning, and memory following in utero marijuana exposure. Moreover, because the amygdala and nucleus accumbens are critical in the development of behavioral and mood disorders, a shift in dopamine receptor expression in these regions following prenatal THC exposure might explain increases in depressive symptoms and impaired social behaviors reported in children upon longitudinal follow-up [45].

Postmortem human studies have also discovered that maternal marijuana use affects fetal expression of opioid-related genes in areas of the brain highly involved in emotional regulation, reward, goal-directed behavior, and motivation [43]. Broadly, opioids influence nociception, motor control, emotions, behavioral reinforcement, and cognition. Altered fetal expression of opioid-related genes can therefore have long-lasting impact on developmental outcomes [44]. Furthermore, alterations in the limbic organization of THC-exposed fetuses, including opioid and dopamine D2 receptor changes in the striatum and amygdala, indicate increased susceptibility for neuropsychiatric impairments in later life.

Prenatal THC Exposure and Neural Circuit Connectivity

During prenatal and postnatal development, CB receptors play a fundamental role in hardwiring the developing brain and contribute postnatally to the regulation of synaptic plasticity throughout the life span [30, 46]. Signaling within the EC system dynamically controls neuronal connectivity during prenatal development in pathways such as the cortico-striatal-thalamic circuitry and several cortical regions involved in addiction and psychiatric disorders [41]. Prenatal cannabis exposure may impact the formation and functions of neuronal circuitries by targeting CB receptors. If EC signaling is significantly altered in the fetus, the loss of particular neurons and glia, cellular redirecting during long-distance migration or interference with synaptogenesis, and disturbed development of neuronal interconnections may lead to subsequent disorder phenotypes [42]. For example, CB1 receptor signaling controls long-range neuronal (e.g., corticofugal, corticospinal) connectivity, and animal studies have shown that prenatal THC resulted in long-lasting alterations in the structure and function of cortical circuitry [46].

Administration of THC to pregnant mice during a demarcated time window disrupts the mouse cortical development, leading to long-term consequences in the fine motor functioning and an increased vulnerability to seizures in the adult offspring [47]. THC exposure may impede the normal development of corticospinal connectivity and increase seizure susceptibility by interfering with CB1R-dependent regulation of both glutamatergic and GABAergic neuron development [47]. This alteration in the corticospinal connectivity is considered to be due to direct impact of THC on the developing embryo, which does not rely on maternal programming and is evident without the need of a secondary insult (e.g., environmental adversity or drug abuse).

Prenatal THC Exposure and Epigenetic Effects

A growing body of evidence suggests that the risk of initiation and progression of a variety of chronic physical and psychiatric diseases depends on epigenetic modifications triggered by environmental signals during early (prenatal or postnatal) life sensitive stages. Epigenetic mechanisms consist of the regulation of gene expression without altering the genetic code. Epigenetic alterations that can regulate gene expression levels consist of DNA methylation, nucleosomal structure and positioning, histone replacement, and small RNA molecules that influence protein production.

Recent studies indicate that cannabis exposure at sensitive periods of development is associated with long-term epigenetic disturbances. The association between prenatal cannabis exposure and addiction vulnerability has been explained, at least in part, by cannabis-induced alterations in the epigenetic regulation of the dopamine D2 receptor (DRD2) gene in the nucleus accumbens. Studies of adult rat brains prenatally exposed to THC showed disturbances in the histone modification profile and decreased D2 receptor mRNA in the nucleus accumbens, which was associated with increased heroin seeking during adulthood [43, 44, 48]. Therefore, cannabis exposure can initiate epigenetic alterations that contribute to long-term disruptions of the D2R in adulthood, predisposing the individual to addiction and other psychiatric disorders [43, 48].

Other evidence exists demonstrating that histone modification plays an important role in the mechanism by which cannabinoids exert immunological effects. Data from various animal models suggests that in utero exposure to cannabinoids results in important T cell dysfunction and a greatly reduced immune response to viral antigens, likely through modifications at the CB2 receptor [49, 50]. Furthermore, evidence from animal studies indicates that the immunosuppressive effects of cannabinoids can be mediated through epigenetic mechanisms such as altered microRNA, DNA methylation, and histone modification profiles. Such studies support the hypothesis that parental or prenatal exposure to cannabis can activate epigenetic changes that could have immunological consequences for offspring as well as long-term transgenerational effects [48, 50–52]. Finally, environmental factors can induce epigenetic alterations in the germ cells that can potentially be transmitted trans-generationally. Germ cells (sperm, oocytes) are also sensitive to cannabinoids, but the exact underlying epigenetic mechanisms remain to be determined [48, 50, 51].

Prenatal Cannabis Exposure and Developmental Effects

Although the relationship between maternal cannabis use during pregnancy and the effects on pregnancy and child outcome is complex, there is increasing evidence from epidemiological and experimental studies suggesting negative effects on the pregnancy and the prenatally exposed individual [53, 54].

The Impact of Cannabis Exposure on the Infant

Cannabis does not appear to produce an increased risk for physical birth defects in exposed infants [54]. Stillbirth [55], shorter gestation lengths, decreased birth weight, and deficits in other growth measures have been reported in some studies [56, 57], although others have shown little to no effect on these birth outcomes [21, 54].

Using the NICU Network Neurobehavioral Scale, a tool to assess infant neurobehavior in at-risk, particularly substance-exposed infants from birth until 1 month of age [58], negative effects of prenatal cannabis exposures indicating neurotoxicity have been reported. These include deficits in visual functioning, tremors, jitteriness, hypotonia, lethargy, and difficulties with arousal and regulation [59, 60]. One Jamaican study found enhanced neurobehavioral functioning; however, possible confounding variables associated with socioeconomic status were reported [61]. Prenatal cannabis exposure has been associated with sleep disturbances during the neonatal period [62] and at 3 years of age [63].

The Impact of Cannabis Exposure on the Developing Child

Evidence for cannabis effects on child growth and development is often difficult to interpret and fraught with confounding factors such as socioeconomic status, psychosocial conditions, and other substance abuse including tobacco use. In longitudinal studies, other confounding factors include genetic vulnerability, parenting and lifestyle issues, economic disadvantage, and stress. However, there are similarities in results of these studies indicating cognitive, behavioral, emotional, and substance use problems in prenatally exposed children and adolescents [64, 65].

Much of the data collected on the effects of prenatal exposure to cannabis come from three longitudinal studies: the Ottawa Prenatal Prospective Study (OPPS) in the 1970s [64, 66], the Maternal Health Practices and Child Development (MHPCD) Study in the 1980s [67–69], and the Generation R (GenR) Study in the early 2000s [70, 71]. The OPPS [59] evaluated a low-risk white middle-class population of 698 pregnant women with 140 selected for follow-up. The use of a low-risk sample that self-reported heavy cannabis use allowed the evaluation of drug effects in relative isolation, without the stressors seen in higher risk populations; but it did not control for nicotine or alcohol exposures. The MHPCD Study [67] followed 564 high-risk, mixed-race pregnant women of low socioeconomic status. The use of a high-risk study group allowed more generalizability of results, but multiple confounders are inherently difficult to fully control for. The GenR Study [70] is a prospective cohort of 9778 multiethnic pregnant women, following 220 who used cannabis during pregnancy, the majority (177) using cannabis only during the first trimester. This study, still in progress, is evaluating the effects of behavior on health including healthcare and maternal determinants for cannabis smoking, and the interplay of factors that can affect both are complex and challenging.

The three studies produced variable results particularly in early childhood development, perhaps due to population differences, differences in dose/potency of THC in the cannabis used, route of administration, and the multiple confounders often affecting child development observations in substance-exposed populations. However, all three noted variable deleterious effects of prenatal cannabis exposure on offspring. Using the Bayley Scales of Infant Development, developmental testing that assesses development in cognitive, language, motor, social-emotional, and adaptive behavior domains, the OPPS found no differences in scores at 12 and 24 months between exposed and non-exposed children, advanced motor skills at 36 months, and lower memory functioning and verbal scores at 48 months in exposed children. At 6 years, exposed children had more impulsivity and hyperactivity, and at 9–12 years, they had impaired visual perceptual functioning [59, 66]. The MHPCD Study [67] found lower Bayley scale scores at 9 months, no differences at 19 months, and lower short-term memory functioning and verbal reasoning in African American participants only at 36 months. At 6 years, cannabis-exposed children overall were more impulsive and hyperactive. The GenR Study found more aggression and inattention for exposed girls only at 18 months, and at 30 and 36 months, no differences between exposed and non-exposed children were observed [70]. However, the literature offers little support for a direct relationship between prenatal or perinatal marijuana exposure and childhood aggression, particularly after accounting for potential confounders.

In opposition to the variability of effects of cannabis on earlier childhood development, prenatal exposure effects for adolescents and young adults have been fairly consistently described. This "unmasking" of earlier deficits [66] with onset of effects during school age or adolescence, especially on executive functioning, may be explained by the theories of "early programming" or the "Developmental Origins of

Health and Disease" [72]. This theory proposes that adverse exposures early in life may reprogram the fetus or infant for immediate adaptation to prenatal and/or neonatal environmental perturbations but enhance the risk of subsequent pathologies. The OPPS found reduced visual perception and increased impulsivity at 9–12 years; decreased concentration, visual memory, and verbal reasoning at 13–16 years; and reduced response inhibition at 18–22 years. The MHPCD Study found diminished abstract and visual reasoning, concentration, internalization, learning and memory, and IQ scores, along with elevated externalization, depression, impulsivity, hyperactivity, and delinquency at 10 years. At 14 years enhanced delinquency persisted, and at 16 years, there was slightly diminished fine motor coordination [73]. The GenR population data for older children has not yet been reported.

Postnatal Cannabis Exposure and Effects on the Developing Child

Maternal Cannabis Use Disorder (CUD)

Acute and chronic effects of cannabis use on the mother are important to consider, as they are likely to affect her ability to care for and develop a relationship with the infant. There are multiple short-term effects of cannabis use that would impact parental care, including impairment of key executive functions such as attention, memory, and decision-making. Impaired judgment, motor coordination, and reaction time have also been associated with impaired driving ability, putting the mother and the unborn/born child or children at risk. In high THC doses, paranoia and psychosis are possible. Some of these impairments have been found to persist after acute intoxication, particularly in chronic users. Effects of long-term or heavy use may include addiction and affiliated behaviors, increased likelihood of depression and anxiety, diminished memory and impaired executive functioning, high-risk sexual behavior, and aggressive behavior during withdrawal [74, 75]. Women with CUD also often have comorbid psychiatric disorders, which may predate cannabis use or result from chronic cannabis abuse.

It is easy to understand how any one of these conditions, or any combination, could harmfully affect the mother's decision-making prior to pregnancy, during pregnancy, or when parenting and could ultimately negatively affect child safety and development. Altered ability to respond appropriately and contingently to infant cues due to periodic changes in consciousness or mood can result in developmental harm, i.e., effects on emerging infant language. Acute effects of THC exposure, combined with risk taking and poor judgment, can result in physical harm to the infant, i.e., inability of the mother to respond appropriately to infant distress. Finally, impairments observed in parenting among women with SUDs may be secondary to the dysregulation of stress and reward-related neural circuits in addiction. The reward-stress dysregulation model of addicted parenting proposes that given anomalous connectivity in brain regions that mediate rewarding vs. stressful cues and experiences, including the nucleus accumbens and amygdala, parenting or caring for a child is less rewarding and more stressful. Women with addiction disorders frequently find normally rewarding infant cues to be stressful, creating a risk for relapse to substance use, which by experience, brings relief from stress [76].

Lactation and the Cannabis-Using Women

As cannabis use in the USA becomes more common, numbers of lactating cannabis-using women and concerns regarding the safety of lactation in cannabis-using women for the child have also increased. There is evidence that chronically cannabis-using women do not decrease use during lactation [77]. Consequently, it is difficult to sort out the effects of postnatal cannabis exposure via breast milk from prenatal exposures, as the two are likely to occur sequentially. It is important to consider that women who use cannabis while breastfeeding are likely to be chronic users who have CUD with reduced control over their use and that postnatal exposures may compound with prenatally acquired deficits. Additionally, there is evidence that lactation care providers are promoting lactation for cannabis users regardless of active or chronic use status 85% of the time [78].

There are several difficulties that face providers when caring for cannabis-using women who desire lactation. The first is unclear and inconsistent guidelines. While AAP and ACOG policies are consistent in advising that cannabis use is contraindicated during breastfeeding [54, 79] as have recommendations from Hale's and LactMed [80, 81], other guidelines have changed to include the possibility of cannabis use during lactation [82, 83]. Current literature includes recommendations for absolute cessation of marijuana use during lactation [84] to continued breastfeeding with concurrent use [85]; however, much of it is based on opinion. Pumping and dumping until maternal toxicology comes back negative for substance use may be prolonged and problematic due to the extended half-life of THC in chronic users [86, 87].

THC readily appears in breastmilk at concentrations up to 7.5 times plasma concentrations and is absorbed and metabolized by the infant [88]; metabolites (e.g., tetrahydrocannabinolic acid) are found in infant stool. THC delivered via lactation to the infant may affect various neurotransmitter systems leading to changes in neurobiological functioning of the infant [24], as described above. Secondhand exposures should also be considered, as THC is present in exhaled breath for 2 h after a single cannabis cigarette, which corresponds to a

newborn feeding schedule. Secondhand exposures may be significant, mimicking active cannabis smoking in extreme circumstances [89].

Studies evaluating effects of cannabis delivered via lactation on infant development are variable. Infant effects including sedation, growth delay, low tone, and poor sucking [90] have been reported. Both effects on motor development [91] and no effects on development [92] have been reported. Infant safety is another concern. Breastfeeding necessarily means that the dyad is in close proximity, and for women with CUD and active cannabis use, this may portend harmful environmental exposure.

Identification and Treatment of Pregnant/Parenting Women with CUD

Based on the effects of cannabis on the mother and concerns about the potential negative effects of maternal marijuana use on the child, there is substantial justification for the implementation of systematic identification and treatment of the mother and child affected by marijuana use. Screening, brief intervention, and referral to treatment are evidence-based approaches to effectively manage substance use disorders.

Optimal identification of CUD and compassionate, nonjudgmental counseling or referral for treatment can have a crucial impact on pregnancy and long-term health outcomes for both the mother and her child. Identifying the pregnant women with a CUD can be difficult. Self-report is the most economic and common method to screen substance use during pregnancy, but maternal interview may be unreliable. In one report evaluating 422 first obstetric visits, 11% of women disclosed any current or past cannabis use, but 27% tested positive for THC. Thirty six percent of the women who were positive for cannabis did not disclose current use [93].

Although disputed by some due to the legal consequences in regions in which marijuana use is banned [94], the American College of Obstetricians and Gynecologists [54] recommends that before pregnancy and during pregnancy, all women should be asked about their use of tobacco, alcohol, and other drugs, including marijuana and other medications used for nonmedical reasons. This committee emphasizes "that the women should be informed that the purpose of screening is to allow treatment of the substance use disorder, not to punish and persecute her. Women need to be informed of the potential consequences of a positive screen, including any mandatory requirements" [54].

Screening tools used in the periconceptional settings are generally questionnaires that are designed to be administered face-to-face by the provider to the woman. They should be administered multiple times during gestation, because patients may be more willing to disclose substance use problems once they develop rapport with a provider [95].

Screening tests can also provide an opportunity to educate the patient. Studies indicate that women frequently use the Internet, social media, friends, or relatives to seek information about marijuana and pregnancy. Pregnant women seeking information regarding gestational cannabis use reported little concrete information from providers [96], and one study showed that the majority (74%) of information delivered was vague and unclear [97]. In another study, nearly half of patients reporting marijuana use during pregnancy received no specific counseling or information, although among those who reported both marijuana and nicotine use, 86% received tobacco counseling [98]. Providers tend to focus more on legal than health risks when counseling pregnant patients and generally believe marijuana to be less harmful than other substances [98]. Consequently, women continue to use cannabis during pregnancy. In one study evaluating 306 surveys of women attending an urban OB clinic, 35% of women reported current use of cannabis and 34% of those women continued to use, with only 27% noting a doctor's recommendation as motivation to quit [99]. Cannabis use in pregnancy is frequently accompanied by the use/abuse of other substances, such as tobacco and alcohol [100].

With changing legal landscapes, the role of the provider in identifying, evaluating, and treating cannabis-using pregnant women has become less clear. There is evidence that providers are more willing to accept cannabis use during pregnancy and lactation [78] largely due to ambiguous information, misperception of risk, lack of training, or scarcity of time or resources to address detected substance use.

Toxicology screening for the determination of drugs and metabolites in maternal and neonatal biological samples offer a more objective and reliable approach; however, there is no good way to understand maternal marijuana use using biomatricies. Neonatal specimens (meconium, cord, and urine) directly reflect fetal exposure to drugs during pregnancy. Urine toxicology testing is most commonly used; however, THC can remain positive in urine drug screens for long periods of time after cessation of use in chronic users. Meconium and umbilical cord testing can detect use during the second and third trimesters but does not differentiate patterns of abstinence closer to delivery and as such are matrices of limited use when evaluating women in substance use disorder treatment. Meconium passage may be delayed up to 5 days after birth, and if passed before birth, drug testing cannot be performed. Newborn toxicology screening primarily focuses on identifying families at risk of ongoing drug use, to address child protection concerns that may be associated with parental drug use and to provide appropriate treatment for suspected cases of withdrawal or intoxication. Synthetic cannabinoids, which are more psychoactive than

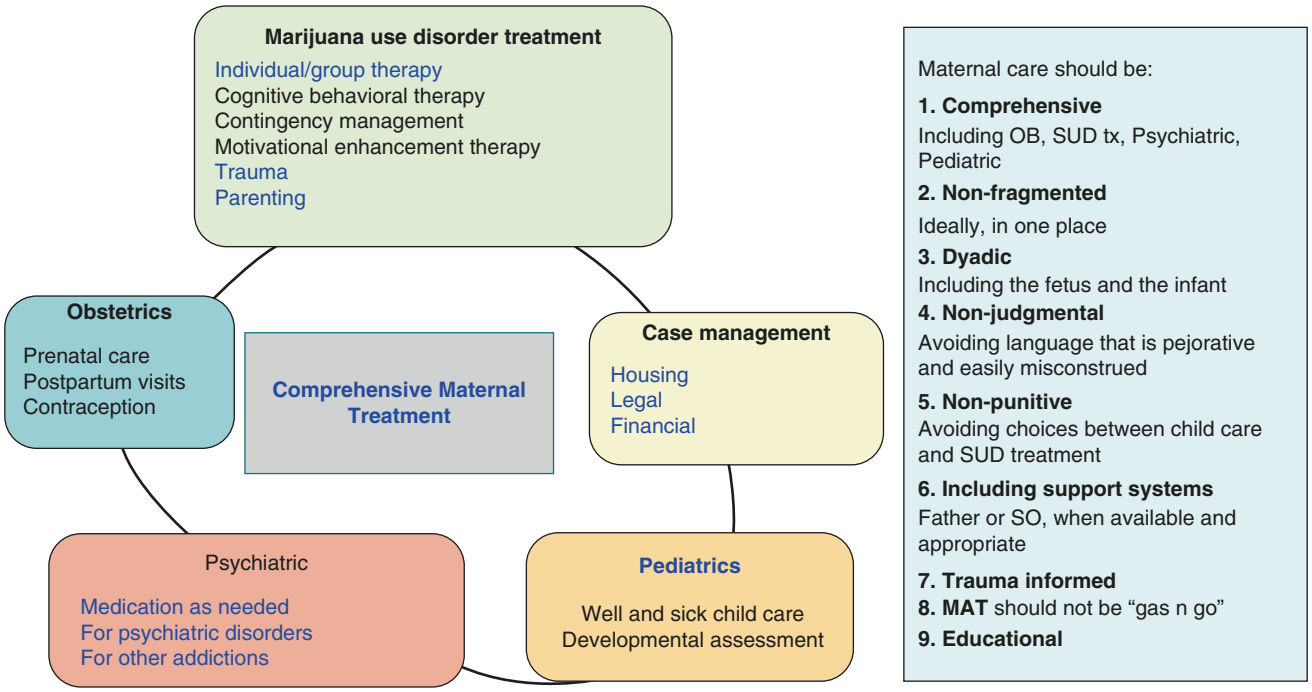

Fig. 17.3 A model of comprehensive treatment for the pregnant woman with a cannabis use disorder

cannabis, are currently non-detectable in standard urine toxicological tests now available.

Achieving abstinence in the treatment of CUD is difficult, and it should be recognized that complete cessation or abstinence of cannabis use is not possible for many women. It has been reported that most marijuana users seeking treatment had multiple quit attempts and perceived themselves as unable to stop [101]. Nevertheless, early detection of a CUD during pregnancy can initiate ongoing support and may produce potentially valuable lifestyle changes that go beyond the perinatal period. It is advised that all pregnant women should be offered screening and support for cessation and relapse prevention at each antenatal visit throughout pregnancy.

Regular users of cannabis may be offered a range of alternate interventions including information, brief intervention, counseling, and psychologically based treatment for cannabis dependency. Pregnant women who are regular users of cannabis or have a CUD should be referred for comprehensive substance use disorder treatment. The proportion of admissions to substance use treatment facilities for pregnant women reporting any cannabis use, in addition to the proportion of admissions for pregnant women reporting cannabis use as a primary substance, has increased dramatically in the last two decades [102].

To date the most successful treatments for CUD have included combinations of motivation enhancement treatment (MET) plus cognitive-behavioral coping skills training (CBT) and/or contingency management (ContM) approaches [75, 103]. In addition to the CUD treatment, the mother will need obstetric and gynecologic care including contraception post-pregnancy, psychiatric evaluation/treatment (if warranted), pediatric care for all children, and referral to necessary services such as housing, legal assistance, trauma-related treatment, etc. (Fig. 17.3).

The CUD intervention should be comprehensive, supportive, and nonjudgmental. Asking the woman to comment on her perceived level of severity may allow for more open discussion of other important problem areas and high-risk situations, which will subsequently allow for the development of strategies for change, including coping with cravings, and goal setting. Treating mental health disorders with standard treatments involving medications and behavioral therapies may help reduce or eliminate cannabis use, particularly among those involved with heavy use and those with chronic mental health disorders. Finally, knowledgeable pediatric care that includes close developmental follow-up and attention to maternal substance use and its effects on parenting and child development should be instituted for all cannabis-exposed children.

Summary

Marijuana use and CUD are common among pregnant and lactating women in the USA. There are several identified mechanisms of potential harm resulting from THC exposure

to the fetus and developing child, and the acute and long-term effects of prenatal THC exposure to child development have been described. It is recommended to minimally advise the cessation of marijuana use for all pregnant and lactating women and to further advise women caring for developing children to continue abstinence. Failing to seek out or to address the problems associated with marijuana use by pregnant and postpartum women when they are identified, regardless of its legal status, is missing an opportunity for intervention for a woman needing treatment, a child at risk for neurobiological and developmental problems, or a dyad at risk for negative outcomes associated with an untreated maternal substance use disorder. Healthcare providers should have training and resources available to be able to screen, identify, and provide readily available and comprehensive treatment for women with CUD in the perinatal period. Additionally, providers should have access to interpretable guidelines based on empirically derived evidence and be able to present a balanced and informed risk assessment to pre-pregnant, pregnant, and postpartum women, with available treatment options for women who may have difficulty abstaining from use.

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Cannabis Use Disorder as a Developmental Disorder

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Abbreviations

CBT	Cognitive behavioral therapy
CUD	Cannabis use disorder
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EFBT	Ecological family-based therapy
NAC	N-acetylcysteine
SUD	Substance use disorder

Overview/Introduction

Despite increasing legalization of cannabis and the emergence of research suggesting potential medical benefits from certain cannabinoid extracts [88], a number of individuals experience negative social, occupational, and physical consequences from chronic cannabis use. An estimated 2.5% of adults in the United States meet criteria for *Diagnostic and Statistical Manual of Mental Disorders* (DSM) 5 cannabis use disorder (CUD) [38]. Consistent with other substance use disorders (SUDs), the prevalence of CUD shows clear age-related trends with a greater prevalence of adults between the ages of 18 and 29 meeting criteria (6.9%) relative to their older adult counterparts (2.5% of 30–44-year-olds and 0.8% of adults over the age of 44) [38]. Initiation of cannabis use, however, often begins in adolescence [28], and rates of CUD are heightened among adolescents [120].

Approximately 3.0% of 12–17-year-olds are estimated to meet criteria for DSM-IV cannabis abuse or dependence [34], and an estimated 6.0% of individuals have progressed to daily or near-daily cannabis use by their senior year of high school [48]. In fact, among high school seniors, there are more daily/near-daily users of cannabis than any other substance [48], and 68.9% of high school seniors report that they do not perceive significant risk in regular cannabis use [48]. However, early initiation is associated with greater risk of developing a CUD [2, 27, 82, 104], and adolescents may be particularly susceptible to detrimental neurocognitive effects of chronic cannabis use [62, 64, 68, 99]. Given the heightened risks associated with chronic cannabis use during adolescence, it is important to understand risk factors associated with adolescent cannabis use and CUD. This chapter will provide an overview of research on developmental trajectories of cannabis use and CUD, neurobiological and environmental factors associated with cannabis use initiation, and factors associated with problematic use at varying life stages, with a focus on adolescence. Finally, the empirical evidence for behavioral and pharmacological treatments for adolescent CUD will be reviewed.

Developmental Trajectories

Cannabis Use Initiation Experimentation with cannabis during adolescence is common. Approximately 45% of high school seniors, 30% of 10th graders, and 13% of 8th graders have used cannabis at least once in their lifetime [48]. In fact, some evidence suggests that more individuals try cannabis for the first time between the ages of 12 and 17 than between the ages of 18 and 25 [2, 28]. Though an estimated 2.5% of individuals meet criteria for a CUD [38], the incidence of CUD increases when only considering those individuals who have tried cannabis [2]. Some data suggests that an estimated 8–10% of individuals who have used cannabis at least once in their lifetime meet criteria for DSM-IV cannabis dependence [2, 65, 82, 110]. However, estimates vary across US national databases, and a more recent survey suggests that 3.5% of individuals who have used cannabis at least once in their lifetime and 11.6% of individuals who have used cannabis in the past year meet criteria for DSM-IV cannabis abuse or dependence [82]. Because initiation is an important modifiable factor in the development of CUD, predictors of initiation are

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discussed briefly here. Large, prospective studies following adolescents through adulthood can distinguish between those individuals who do and do not initiate cannabis use. For example, a study by Epstein et al. [25] found evidence for four groups of adolescent/young adults: chronic cannabis users who initiated use in adolescence and maintained use throughout early adulthood, adolescent-limited users, late-onset users, and nonusers [25]. The late-onset and nonuser groups had fewer peers who used cannabis at ages 14 and 18 and less neighborhood disorganization at age 18 compared to the chronic use and adolescent-limited use groups, suggesting environmental factors differentiated those who used cannabis in early adolescence from those who did not [25]. Though there is evidence that males are more likely to initiate use, this appears to be a function of differential access to cannabis across genders [111]. It should again be emphasized, however, that initiation of cannabis use in adolescence is common and to some extent, normative. In fact, some studies suggest that older adolescents and young adults who have occasionally experimented with cannabis function at least as well in certain social and cognitive domains than individuals who have never experimented with cannabis [90, 91]. Other factors such as the frequency of cannabis use and timing of initiation may be more important predictors of risk for CUD.

Early-Onset vs. Late-Onset Cannabis Use In particular, earlier cannabis use initiation appears to be associated with worse psychiatric and cognitive functioning [45, 114, 62]. Prospective data from adolescents in New Zealand suggested that 21.7% of adolescents who initiated cannabis use by age 16 met criteria for DSM-IV cannabis dependence by age 21, though the overall rate of cannabis dependence in the full sample was 9% at age 21 [27]. Similarly, data from the United States suggests that adolescents who have used cannabis prior to age 15 have almost double the odds of developing a CUD relative to those who initiated cannabis use later in life [82]. Thus, early age of initiation of cannabis use is also a strong predictor of later CUD. This is consistent with findings from several other studies. For example, Epstein et al. [25] found that individuals who engaged in early-onset cannabis use which persisted into adulthood reported greater CUD symptoms at age 33 than individuals with late-onset cannabis use. Finally, two studies found that age of cannabis use initiation was unrelated or even positively related to later cannabis use problems/CUD once controlling for other variables such as frequency of cannabis use in mid-adolescence [24] or demographic characteristics, psychiatric comorbidity, and substance use covariates [65]. This suggests that the association between age of initiation and later CUD may be due to the fact that adolescents who initiate cannabis use earlier also have other significant risk factors and quickly progress to frequent use.

Consistent with these findings, earlier initiation of cannabis use may also be associated with increased psychiatric and substance use comorbidity and lower general functioning. Those who initiated cannabis use in early adolescence reported greater depressive symptoms ([25]; see [24] for an exception), past-month alcohol use [25], and past-year use of controlled substances [24]. Age of initiation also predicted outcomes in adulthood. Early-onset users reported more alcohol and tobacco use disorder symptoms and lower income and educational attainment in adulthood [25]. Another longitudinal study identified trajectories of cannabis use from early adolescence to mid-adulthood (age 14 to 43) in a community-based representative sample of 548 individuals [11]. They classified individuals based on six empirically derived cannabis use trajectories. Two of these trajectories included "chronic/heavy users" who began cannabis use by age 14 and escalated and maintained use through adulthood (3.6%) and "increasing users" who showed no or infrequent cannabis use at age 16 but continually escalated and maintained use through adulthood (5.1%). The "chronic/heavy user" group may serve as an approximate estimate of early-onset CUD, while "increasing users" may serve as a proxy for late-onset CUD. Compared to a nonuser/experimenter group, "chronic/heavy users" (early onset) reported more symptoms of emotional dysregulation in adulthood, but the "increasing users" (late onset) did not. In contrast, "increasing users" (late onset) reported greater sensation seeking in adulthood relative to nonusers/experimenters, but "chronic/heavy users" (early onset) did not.

In sum, existing data suggest that those who engage in earlier onset use are at increased risk for CUD and tend to have more negative substance use, psychiatric, and general outcomes [11, 24, 25].

Time-Limited Versus Chronic Cannabis Use Most adolescents who try cannabis do not progress to heavy or chronic cannabis use. However, consistent with other externalizing behaviors, even engagement in problematic substance use is often time-limited [15, 72]. The drop in prevalence of CUD among adults older than 29 [38] supports the notion that a large proportion of individuals do not persist in their problematic cannabis use. There are multiple potential reasons for the observation of adolescent/young adult-limited CUD. First, sensation seeking and risk taking are thought to peak around age 15, which is consistent with the rapid neurobiological development of subcortical regions of the brain occurring during this period [14, 103]. (This is discussed in more detail later in the chapter.) Second, as adolescents are striving to achieve more independence, substance use involvement may be viewed by adolescents as a way of asserting their independence [72]. Third, as role transitions occur requiring more responsibility (e.g., transition to full-time employment or parenthood), reduction of substance use

is evident (e.g., [51]). This is often referred to as "maturing out" of substance use. However, the extent which "maturing out" explains declining rates of SUDs after early adulthood has been questioned [109].

During adolescence, it can be difficult to differentiate which adolescents are likely to develop a chronic CUD, as patterns of use may be comparable between adolescent-limited users and chronic, lifetime users. White et al. [115] used longitudinal data from the Pittsburgh Youth Study, a study which followed males from first grade to age 29 [115]. Restricting their sample to those who used cannabis at least monthly during a full year between age 14–17, they compared men who "matured out" of cannabis use (i.e., reported no use at ages 26 and 29) to those who used at least weekly at age 26 or 29 on measures of adolescent attitudes toward cannabis/delinquency, impulsivity, depression, alcohol use, tobacco use, other drug use, peer cannabis use, parental monitoring, childhood maltreatment, and family/neighborhood factors. No predictors assessed during childhood or adolescence distinguished between the men who matured out and the men who persisted in their cannabis use.

In contrast, other longitudinal studies have found some differences between those who engage in adolescent-limited cannabis use and those who persist in use. Epstein et al. [25] compared adolescent-limited users to those who engaged in chronic use beginning in adolescence. The chronic cannabis use group had significantly higher self-reported behavioral disinhibition beginning at age 14, which persisted at age 18, 21, and 24. Not only did disinhibition precede regular use, but it distinguished between those who would "mature out" by age 30 and those who would persist in chronic, heavy use. The adolescent-limited group had significantly higher levels of disinhibition than nonusers, however, and this effect also persisted at each time point. Similarly, Passarotti et al. [75] followed 1204 adolescents from 9th and 10th grade (mean age~15.5) to approximately age 22.5 (6 year follow-up) [75]. The majority of adolescents had low to moderate use (i.e., using cannabis less than once per week, on average) at baseline. They compared adolescents who escalated in their frequency of cannabis use over time (8.3% of total sample) to adolescents whose use remained relatively constant at low to moderate levels of use through early adulthood (52.5% of total sample). Those who escalated in their use, on average, approached near-daily use at the 6-year follow-up. "Escalators" and "non-escalators" did not differ in average frequency of cannabis use at baseline. However, "escalators" reported higher novelty seeking and aggression/antisocial behavior at baseline than the non-escalating group, and these differences were stable across time. No differences in reported depressive symptoms were found. "Non-escalators" reported higher stress at baseline than escalators, but there were no group differences in stress levels at 6-year follow-up. A third prospective study also found that chronic cannabis users, relative to other groups, had higher sensation seeking, more externalizing behaviors (e.g., aggression/delinquency), and lower self-control [10].

In sum, though evidence is mixed, there is some evidence to suggest that adolescents with early, elevated disinhibition, sensation/novelty seeking, and externalizing behaviors are more likely to persist in their use throughout early and later adulthood and this is consistent with theoretical models [72]. However, a limitation of most of this existing work is that frequency of cannabis use is examined, rather than persistence of problematic use. Data from a nationally representative sample of US citizens suggested that impulsivity in early adolescence was the only childhood/adolescence predictor of adult CUD, after controlling for more proximal factors such as psychiatric and substance use disorder comorbidity [8]. Child/adolescent data was obtained retrospectively, however. Kosty et al. [59] recently published a prospective study examining trajectories of CUD from age 14 to 30 in a regionally representative sample of adolescents/young adults in western Oregon. Three classes were empirically derived: (1) a class for whom risk for CUD persistently increased across development (7% of the sample), (2) a "maturing out" class for whom CUD risk peaked in the early twenties and subsequently declined (9% of the sample), and (3) a class with stable, low risk (84% of the sample). The "maturing out" class and the persistent, increasing risk class did not differ in terms of psychiatric disorders prior to age 14 (internalizing or externalizing), in rates of childhood maltreatment, or in family characteristics (i.e., dual vs. single parent household). However, males were more likely to fall in the persistent, increasing risk class relative to the "maturing out" class. Differences in psychiatric functioning between these two groups did not appear until age 24 to 30, at which time the persistent, increasing risk class endorsed more externalizing psychiatric disorder and psychotic symptoms [59]. In contrast with theories of adolescent-limited externalizing behavior [72], Kosty et al. [59] found that the "maturing out" class had an earlier age of CUD onset as compared to the class with persistent, increasing risk for CUD. These data suggest that psychiatric comorbidity may be associated concurrently with increased risk for CUD; however, prospectively predicting who may develop a CUD from adolescent psychiatric disorders appears to have limited utility. Further research examining prospective predictors of CUD risk across the life span are critical.

CUD in Later Adulthood In contrast to the high rates of CUD in adolescence, rates of CUD are the lowest among middle-aged and older adults [16, 38, 39]. Estimated rates of CUD have increased from 2001–2002 to 2012–2013 in all adult age groups, however [39]. Among middle-aged and older adults who meet criteria for a CUD, psychiatric

comorbidity and medicinal use of cannabis may be particularly high [16, 17]. In a nationally representative sample of adults in the United States, adults age 50 and older who met criteria for a CUD were more likely to have a comorbid psychiatric or substance use disorder, particularly an anxiety disorder, posttraumatic stress disorder, bipolar disorder, or an alcohol or other drug use disorder, relative to adults 50 and older who used cannabis in the past year but did not meet criteria for a CUD [16]. Adults with a CUD were also more likely to endorse interpersonal stressors, debt, and workplace problems. Rates of past-year cannabis use are relatively low in this age group; however, the past-year cannabis use group is not a representative comparison group. Only an estimated 3.9% of adults 50 or older endorsed any past-year cannabis use [16]. Interestingly, *any* cannabis use in older adulthood was associated with an increased rate of comorbid psychiatric disorders [16, 35, 87].

Neurobiological Risk Factors

Several models of addiction posit that there are underlying neurobiological risk factors that increase risk for the development and/or maintenance of substance use disorders. These models often include deficits in response inhibition and planning/impulsivity, deficits in emotion regulation or negative reinforcement motives for substance use, and heightened sensitivity to the rewarding properties of the substance or heightened salience of drug-related cues as etiological risk factors [29, 60, 61, 93]. Each of these neurobiological risk factors is discussed in terms of the development of CUD.

The heritability of CUD may be at least partially explained by the heritability of these risk factors or "endophenotypes." The interested reader is referred to Chapter 3 for a thorough discussion of genetic influences on CUD. Relevant to the current topic, the influence of genetics versus environment can vary with age. Though environmental risk factors have a larger impact on cannabis use during adolescence, as individuals age, genetic factors become more important predictors of cannabis (and other substance) use outcomes [54]. Heightened genetic and/or neurobiological risk may decrease the likelihood that an adolescent "matures out" of cannabis use or CUD. Disinhibition/impulsivity, stress/affect regulation, and heightened sensitivity to the rewarding properties of substances may also be related to CUD persistence into adulthood.

Disinhibition/Impulsivity Impulsivity is a broad, multifaceted construct used to describe deficits in self-control, an inability to inhibit a response, rash action while experiencing extreme positive or negative emotions, or preference for immediate gratification or reward [21, 26, 116]. The breadth of the construct of impulsivity and variation in its measurement make it difficult to make clear conclusions about associations between cannabis use and impulsivity. However, most comprehensive theoretical models of addiction acknowledge that impulsivity is a risk factor for problematic substance use. Impulsivity has consistently been shown to be associated with risk for substance use disorders and earlier-onset substance use (e.g., [44, 92, 108]). Impulsivity is also related to treatment outcome for CUDs among adolescents [7, 101] and adults [13], with higher impulsivity resulting in worse treatment outcomes (see [77] for exception).

Impulsivity/disinhibition is thought to be the result of underactive executive control in the prefrontal cortex [14]. Impulsivity peaks at age 10, on average, and declines thereafter [103]. Sensation seeking is an independent but related construct associated with increased risk taking and reward seeking. Sensation seeking is thought to be driven by subcortical regions of the brain (e.g., amygdala), which develop more quickly than the prefrontal cortex, and it peaks around age 15 and declines thereafter [14, 103]. Risk taking and substance use initiation are most evident when the prefrontal cortex development lags behind the rapidly developing limbic system [14]. Heightened risk for CUD during adolescence corresponds with heightened impulsivity and sensation seeking evident in adolescence [79]. Impulsivity and sensation seeking decline at different rates across people [37, 79], however, and those who show a slower rate of decline in impulsivity show a more rapid progression in cannabis use from adolescence to adulthood [79].

Because impulsivity is multifaceted, numerous attempts have been made to determine which aspects of impulsivity are related to problematic cannabis use. One study found that self-reported impulsivity, but not a behavioral measure of risk taking, was associated with frequency of adolescent cannabis use [78]. It is not uncommon for self-report impulsivity measures and behavioral tasks thought to measure impulsivity-like constructs to show poor agreement [20]. Among adolescents, impulsive action when experiencing strong positive (e.g., positive urgency) and negative (e.g., negative urgency) emotions [21] was related to problematic cannabis use in a nonclinical sample of 16–18-year-old students [102]. In a clinical sample of adolescents (ages 12–18) seeking treatment for substance use problems (with cannabis being the most frequently used substance), only negative urgency was associated with increased frequency of cannabis use and increased problems due to substance use [106]. Negative urgency may also reflect risk for affective disorders, such as depression in preadolescents [98], and is perhaps an indicator of multiple overlapping risk factors (see later discussion of stress/affect regulation as a risk factor for CUD).

In addition to considering impulsivity/disinhibition as an etiological pathway to CUD, it is also important to consider

that impulsivity/disinhibition may result from acute cannabis intoxication. Research examining age-related associations between acute cannabis use and disinhibition is limited. In one laboratory-administration study, adolescent males (ages 16–17) committed more errors on a stop-signal task (i.e., response inhibition) following administration of cannabis (relative to placebo) than did young adult males (ages 24–28). Interestingly, this effect occurred despite the fact that the adolescents were slightly more frequent users of cannabis, on average, and that the cannabis dose was adjusted based on body weight [73]. However, this same study showed that adults had greater cannabis-induced deficits in spatial working memory, verbal memory, and slower reaction times [73]. These findings suggest that indicators of acute cannabis intoxication may be age-specific. This study also suggests that acute cannabis intoxication may further exacerbate already heightened disinhibition among adolescents.

Stress/Affect Regulation Consistent with research suggesting that impulsivity in response to negative emotional states is related to more problematic cannabis use, adolescents who use cannabis to relieve aversive states, such as stress or negative affect, experience more problems due to cannabis use [1]. Negative reinforcement, or the removal of unwanted negative states, is often a motivation for substance use [5, 58], and cannabis use is no exception [94, 95].

The expectation that cannabis will alleviate negative emotions may be enough to drive use, even if cannabis does not have the intended effect. In the laboratory-administration study conducted by Mokrysz et al. [73] referenced above, adolescents did not show an anxiolytic effect of acute cannabis administration (and, in contrast, the young adults reported increased anxiety following use). A naturalistic study utilizing ecological momentary assessment to examine affective antecedents and consequences of cannabis use in the daily lives of adolescents who regularly used cannabis found that negative affect increased in the first hour following cannabis use, relative to pre-cannabis use, but this effect was time-limited [85]. Interestingly, the effect was most pronounced among adolescents who reported that they used cannabis to help them cope with negative emotions or to conform. Using cannabis to cope with negative emotions or to conform was the reported motive in approximately 10% of all episodes of cannabis use in this sample [85]. Thus, negative reinforcement cannabis use was still relatively infrequent.

In certain populations, such as among individuals with depression or anxiety, negative reinforcement cannabis use may be more frequent. Indeed, anxiety and mood disorders are common among individuals with a CUD (e.g., [53, 118]). Some researchers have argued that comorbid CUD and psychiatric disorder is largely a result of the effect of cannabis on anxiety and mood, rather than a result of individuals using cannabis to self-medicate [119]. Supporting this, several studies have shown that heavy cannabis use preceded mood and anxiety disorders developmentally [9, 76]. However, negative reinforcement substance use is more common as addiction progresses [58]. With continued use, substance withdrawal can produce stress/negative affect which elicits continued substance use to alleviate symptoms of withdrawal [5]. Thus, an individual's motivation to use cannabis may evolve as CUD progresses, and both (a) worsening mood and (b) increased negative reinforcement use (self-medication with cannabis use) are to be expected as CUD progresses [5, 57, 58]. Thus, affective dysregulation may be a consequence of CUD and also contribute to the maintenance of CUD via negative reinforcement use.

Sensitivity to Reward/Pharmacological Vulnerability Perhaps not surprisingly, it has been proposed that individuals who have more positive and less negative responses following acute administration of a substance are at increased risk for problematic use. The more reinforcing one's initial experiences with cannabis, the greater the likelihood that they will seek it out in the future. Subjective response following substance administration has been extensively studied in the development of alcohol use disorders. Individuals who report more stimulating effects from alcohol during the early phase of a drinking episode and fewer sedating effects during the later phase of a drinking episode may be at increased risk for problematic use [81]. Subjective response to cannabis is more difficult to study given that pharmacological effects differ at different concentrations and variations of cannabinoids [18, 66]; however, the cannabinoid receptor, CB1, has been linked to cannabis-induced reward [18]. Though several laboratory-based administration studies have documented subjective and physiological response to cannabinoids (e.g., [36, 52, 66, 80, 89]), few have examined individual differences in subjective and physiological responses to cannabis administered in the laboratory as a risk factor for the development of CUD. However, a longitudinal study found that adolescents who retrospectively reported cannabis effects as more positive during early exposures (prior to age 16) were significantly more likely to report symptoms of DSM-IV cannabis dependence from ages 16 to 21 [27]. One laboratory-administration study examined differences in subjective and cognitive effects of cannabis between adolescent and adult males. In this study, adolescent males had blunted reactivity to cannabis relative to young adult males and were less likely to report feeling "stoned" or feeling the effects of the cannabis, relative to the adult males [73]. The adolescents also reported increased craving following administration of cannabis or placebo, while the adults reported increased satiation. The authors suggest that the decreased physiological and subjective effects and increased desire to use cannabis following administration

may put adolescents at increased risk for further drug administration [73]. Participants in this study were already regular users of cannabis, but did not endorse symptoms consistent with CUD. Overall, these findings suggest that early positive experiences may encourage future use and potentially be a marker for CUD risk. However, adolescents may find cannabis less impairing than adults, which also may encourage continued and heavier use.

Environmental Risk Factors

A number of environmental risk factors for CUD have been considered, such as childhood physical/sexual abuse and neglect, family factors, peers, and neighborhood characteristics. In particular, parental and peer relationships may influence the likelihood of cannabis use initiation and, consequently, escalation to CUD. Based on social learning and social control theories, relationships with both parents and peers are crucial for predicting adolescent drug use [4]. Initial research finds that adolescents who spend time with adults who use cannabis are more likely to become early-onset cannabis users. Parental attitudes toward cannabis use significantly predict adolescent cannabis use. Adolescents who see their parents engage in drug use may be more inclined to experiment with their own drug use, maintain accepting attitudes toward drug use, and choose friends who are drug users [4]. Studies have shown that recent parental cannabis use is associated with the initiation of adolescent cannabis use within the next year [69] and the persistence of chronic cannabis use into adulthood [113]. Adolescents with parents who maintain strict rules about cannabis use have a decreased likelihood of initiating cannabis use. Parents who maintain authoritative parenting styles produce adolescents with lower likelihood of initiating illicit drug use [12]. Increased parental monitoring also decreases the likelihood of initiation of regulated substances. At younger ages, family relationship quality (shared activities, mutual regard, and positive affect) with increased parental monitoring is a significant predictor of a lower likelihood to engage in cannabis use [86]. Alternatively, indulgent or permissive parenting styles increase the likelihood of adolescents using cannabis much like neglectful parenting [12]. Maltreatment from neglectful parenting leads to a vulnerability to several psychopathological disorders. Rogosch et al. [84] found evidence suggesting higher rates of substance abuse and dependence among maltreated individuals.

In addition to parental factors, peer relationships can influence an adolescent's exposure to deviant peers and regulated substances (such as cannabis) later in adolescence. While initial parental monitoring contributes significantly to the initiation of adolescent cannabis use, there is evidence that parental influences decrease in significance once peer influences are considered [4]. By the time adolescents reach high school age, deviant peers begin to grow in significance as a predictor of substance use and ultimately become the strongest predictor during early adulthood [86]. As adolescents continue to develop, their choice of peers greatly impacts their likelihood to engage in cannabis use. Those who choose to interact with more deviant peer groups are more likely to be exposed to substances like cannabis. While early parenting practices can help influence acceptable peer groups, once the peer groups have been chosen, adolescents begin to rely heavily on their experiences with friends. Based on a study conducted by Mason and colleagues, it can be reasoned that a direct invitation to use substances from a peer carries influence, particularly if an adolescent is attempting to become established or to fit in with an aspiring peer group [67]. The same study found that those who were offered cannabis at age 13 were more likely to have used the substance by age 15 [67]. While peers may directly influence cannabis use, it has also been suggested that adolescents tend to select friends who are similar to them and share their own cannabis use preferences [22]. Finally, though peers may be influential in initiation of cannabis use, at least one study showed that solitary cannabis use in adolescence is an indicator of greater cannabis-related problems [19].

In sum, parental and peer factors may influence cannabis use initiation, which may expedite or prevent transition to a CUD among those with other predisposing risk factors [55, 56].

Treatment Considerations for Adolescents with CUD

It is important that treatments for CUD take into account the developmental stage of the individual. Other chapters in this book (Chapters 19–25) serve as a great reference for the most up-to-date research on treatments for CUD, primarily for adults. Therefore, we provide a summary of existing research on treatment for adolescent CUD. Many reviews on behavioral and pharmacological adolescent SUD treatment exist, and the interested reader is referred to these reviews for more in-depth information [31, 33, 43, 71].

With regard to behavioral treatments, Hogue et al. [43] reviewed literature on adolescent (ages 12–19) outpatient treatments for substance use problems. Though many of the reviewed studies did not distinguish cannabis from other substance use (as many outpatient treatment settings do not offer unique programming based on the primary problematic substance), several studies showed reductions specific to cannabis use [83, 100, 117]. A treatment was considered well-established if efficacy was demonstrated in at least two different settings by two independent research teams. A treatment was considered probably efficacious if only one rigorous, randomized controlled trial supported the efficacy

of the treatment (or only one group of investigators). Based on these criteria, group and individual cognitive behavioral therapy and ecological family-based treatment were considered well-established. Motivational interviewing and behavioral family-based treatment were considered probably efficacious.

Cognitive behavioral therapy (CBT) is aimed at modifying problematic thoughts and behavioral responses. It has been shown to be effective in reducing adolescent substance use in both group [6, 49, 50, 112] and individual formats [3, 23, 40, 96]. Ecological family-based therapy (EFBT) is a term that encompasses several models of therapy that intervene with youth and their families at home and community settings. Multidimensional Family Therapy [63, 107] and Multisystemic Therapy [41, 42] are two examples of EFBTs. EFBTs have been shown to be equivalent to other established treatments for adolescent substance use and superior to treatment as usual [40, 96, 97]. Motivational interviewing is a therapy designed to enhance an individual's commitment to change their substance use behavior by building on principles of motivation and self-efficacy. At least one study found that motivational interviewing was equivalent to other established treatments [96]. Finally, behavioral family-based therapy is an in-office treatment which aims to modify family interactions, and one study found it to be equivalent to individual CBT [3].

Though behavioral treatments are often the first treatment option for adolescents with problematic cannabis use, several pharmacological options have been tested as potential adjunctive treatments. No FDA-approved medications for CUD (adolescent or adult) exist to date. Two randomized controlled trials testing the efficacy of pharmacological interventions for adolescent CUD/cannabis dependence have been conducted.

N-acetylcysteine (NAC), an over-the-counter antioxidant that impacts glutamatergic functioning, has been examined as a potential adjunct to contingency management for adolescent (ages 15–21) DSM-IV cannabis dependence [30]. In addition to weekly cessation counseling and contingency management which provided monetary reinforcement for negative urine drug tests, adolescents (N = 116) were randomized to receive NAC or placebo (1200 mg twice daily) in a double-blind fashion. The NAC group had approximately double the odds of abstinence at the end of the 8-week treatment period. However, there were no differences between groups at 1-month follow-up. Interestingly, NAC has also been examined as a cessation aid for adults (age 18–50) with CUD, but it was not found to be superior to placebo in promoting abstinence [32]. Because the adolescent and adult NAC trials had overlapping age ranges, it was possible to examine whether NAC was more effective among 18–21-year-olds in the adult NAC trial. Though not statistically significant, the odds ratio was similar to that observed in the adolescent trial for the 18–21-year-old subgroup. Thus, NAC (discussed in more detail in Chapter 22) may be a promising pharmacological option for adolescent CUD. However, future research is needed to clarify the age-related effects and to determine which adolescents may be most likely to benefit.

Topiramate has been shown to be effective in adult clinical trials for non-cannabis substance use disorders [46, 47, 74]. Thus, Miranda et al. [70] have examined topiramate as an adjunct to motivational enhancement therapy for adolescents (15–24) with problematic cannabis use. In this study, 66 adolescents were randomized to receive topiramate or placebo for 6 weeks (titrated up to 200 mg/day until week 4). Though topiramate plus motivational enhancement therapy reduced quantity of cannabis used, there was a significant side effect profile which suggested that it was not well-tolerated by many adolescents [70].

Findings from these two pharmacological studies further support the need for adolescent-specific clinical trials to test the efficacy of prospective treatments for this population. At this time, behavioral treatments for adolescent CUD have received more research attention and support, but NAC is a pharmacological treatment that shows promise.

Summary and Conclusions

CUD shows strong age-related trends, and adolescence is a high-risk time for cannabis initiation and CUD onset. Earlier onset of initiation is associated with increased CUD risk and worse neurocognitive functioning, perhaps because heavy cannabis use interferes with normal brain development during a critically sensitive period of brain maturation. Future longitudinal, prospective studies are needed to clearly identify the neurobiological antecedents and consequences of chronic cannabis use. For some, cannabis use and CUD are limited to the adolescent years. Psychopathology and poorer general functioning are associated with the persistence of CUD into adulthood. Though middle-age and older adults have a lower overall risk of CUD, comorbid psychiatric conditions are common among older adults who do meet criteria for CUD.

A number of neurobiological and environmental factors exist that contribute to the development of cannabis use initiation and CUD. Heightened disinhibition/impulsivity, high stress coupled with a lack of adaptive coping mechanisms, and more positive/fewer negative initial experiences with cannabis may increase the likelihood of developing a CUD. Exposure to parental substance use, low parental monitoring, child maltreatment, and association with peers who use cannabis may also contribute to CUD development.

Treatment approaches for CUD should consider the developmental stage of the individual. Behavioral treatments are

often the first approach for adolescent CUD, but pharmacological options such as N-acetylcysteine hold promise. Treatment outcomes may be improved if the treatment is matched to the underlying neurobiological and/or environmental risk factors that predispose an adolescent to CUD or maintain the symptoms of CUD [29, 105]. As our ability to assess individual-level CUD risk and maintaining factors improves, we will be able to develop interventions that directly address individual-specific factors in a personalized way.

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Cannabinoids to Treat Cannabis Use Disorders

19

Christina A. Brezing and Frances R. Levin

Introduction

Given the success of agonist treatments for nicotine and opioid use disorders and antagonist treatment (naltrexone) for opioid use disorders, conceptually similar treatments have been explored for cannabis use disorder (CUD). Δ-9-tetrahydrocannabinol (THC) is the primary compound responsible for the subjective, behavioral, and cardiovascular effects of cannabis [6]. These effects are mediated by the endocannabinoid receptor CB-1 (cannabinoid receptor 1) [18]. Cessation of cannabis use leading to the abrupt absence of THC following chronic administration produces an abstinence syndrome characterized by withdrawal symptoms including anxiety, mood changes, craving, insomnia, and anorexia [4]. Withdrawal is thought to contribute to difficulty in achieving abstinence from cannabis use and early occurrence of relapse [4]. Cannabinoids with THC agonist properties not only have the benefit of suppressing withdrawal but also may attenuate the acute effects of drug use. The former is key in preventing relapse during quit attempts and the latter in initiating and maintaining abstinence or reduced use. Generally, an ideal THC agonist substitute in the treatment of CUD has the following properties that are consistent with a harm reduction treatment strategy: has low abuse potential, has less hazardous route of administration, functions to reduce withdrawal symptoms and craving, decreases the reinforcing effects of cannabis and THC, and leads to an improvement in functioning [2].

The use of antagonist approaches by directly decreasing the subjective and reinforcing effects of a drug of abuse has demonstrated success in the treatment of other substance use disorders as well. Rimonabant is a high-affinity CB-1receptor antagonist that showed promise in the human laboratory as a possible treatment for CUD. However, the serious adverse psychiatric effects of rimonabant including anxiety, depression, and suicidality leading to the discontinuation of its use in clinical trials preclude further investigation or feasibility of its role in the treatment of CUD [22]. This early promising work may have paved the way for the development of CB-1 receptor antagonists with different properties that demonstrate effectiveness in initiating abstinence or preventing relapse to cannabis use without the adverse clinical effects. This chapter will present the clinical studies performed to date in both the human laboratory and clinical treatment settings of the clinically available cannabinoids and cannabinoid antagonist (rimonabant) in the treatment of CUD.

CB-1 Receptor Agonists

A number of human laboratory studies have looked at dronabinol, an oral THC, which has FDA indications for the treatment of anorexia associated with AIDS and second-line treatment for nausea and vomiting associated with cancer chemotherapy in doses up to 20 mg per day. Hart et al. [14] evaluated the dose effects of dronabinol on subjective effects of smoked cannabis. This study found that 80 mg, but not 40 mg, attenuated the subjective effects of smoked cannabis, noting a 50% reduction in "good effect." Haney et al. [10] was the first to look at oral THC and its effects on cannabis withdrawal and a model of relapse, defined by subjects choosing to purchase with study earnings and self-administer smoked marijuana after a period of abstinence in the inpatient lab setting.

The authors found that dronabinol (40 mg) decreased certain withdrawal symptoms including craving, decreased food intake, physical symptoms, and mood disturbance, without producing intoxication, but failed to prevent relapse as compared to placebo [10]. Budney et al. [5] looked at two doses of dronabinol (30 mg and 90 mg per day) in an outpatient

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human laboratory study of nontreatment-seeking heavy cannabis users. The authors found that while both doses reduced withdrawal symptoms, the higher dosage (90 mg/day) produced additional suppression of withdrawal symptoms such that ratings returned to baseline when participants were smoking as usual (i.e., participants did not experience withdrawal symptoms on high-dose dronabinol) [5]. Vandrey et al. [26] examined dose effects of dronabinol. The authors found that dronabinol dose dependently decreased withdrawal symptoms with few adverse effects or problems with cognitive performance [26]. Surprisingly, this study did not demonstrate any alteration in subjective effects of smoked cannabis on any dose, as was previously found in Hart 2002 [14], though attenuation in increases in heart rate was seen. In summary, the human lab studies of oral THC have some mixed results regarding its impact on subjective effects of smoked cannabis in addition to failing to prevent relapse, though provided strong evidence for the role of oral THC (dronabinol) in dose dependently attenuating withdrawal at higher than FDA-approved doses in nontreatment-seeking, heavy cannabis users.

Building off of the human laboratory data of cannabinoid agonists, Levin et al. [19] studied dronabinol in a fully powered placebo-controlled trial for the treatment of CUD. Primary cannabis outcomes included self-report of use as measured with the timeline followback (TLFB). While urine was collected for cannabinoid testing in the placebo group to correlate self-report, urine results in the dronabinol group were not used due to the medication's confounding effects on urine cannabinoid testing. Levin et al. [19] found no effect of dronabinol on abstinence compared to placebo, though withdrawal symptoms were significantly lower and study retention was greater (77% vs 61%) on dronabinol compared to placebo. Notably, pretreatment withdrawal symptoms were not assessed to provide a baseline measure to compare to results during treatment. The comparison of dronabinol to placebo with regard to withdrawal also included all study participants and not just those who reduced or abstained from cannabis, suggesting that changes in "withdrawal" may be encompassing other factors as well. As a result, it is difficult to assess the magnitude with which dronabinol suppressed withdrawal; however, given the limitations, the findings are consistent with the human lab findings and suggest a useful role of dronabinol in the treatment of cannabis withdrawal.

Haney et al. [9] looked at oral THC in conjunction with lofexidine for its effects on cannabis withdrawal, craving, and relapse in the human lab. Given some of the earlier identified limitations of oral THC as monotherapy, combination medication strategies were pursued hypothesizing that synergies in multi-mechanism approaches may effectively reduce withdrawal and ultimately impact cannabis use by preventing relapse. Lofexidine was selected because of its reported favorable side effect profile compared to other alpha-2 adrenergic agonists (e.g., clonidine, guanfacine) in conjunction with preclinical data demonstrating that noradrenergic hyperactivity contributes to withdrawal from cannabinoids [13]. The study found that THC alone again decreased a subset of withdrawal symptoms but failed to decrease the laboratory model of relapse. Lofexidine alone was found to have side effects of sedation and worse abstinence-related anorexia but did improve sleep and decrease relapse to smoking cannabis. As hypothesized, the combination provided the most robust improvements in sleep, reductions in cannabis withdrawal, craving, and relapse with 50% of the participants choosing not to purchase any puffs of cannabis for the duration of the relapse phase [9].

Following the robust results of this human lab study, Levin et al. [20] took the combination of dronabinol and lofexidine to the clinic setting. This time, however, there was a discrepancy between the lab and clinic setting findings. There was no difference between active medication and placebo with regard to self-reported rates of abstinence, and both groups showed reductions in cannabis use over time with half of all patients reporting a reduction in use of 50% or more [20]. There was also no difference in withdrawal scores over time. There was an overall low percentage of participants completing the medication phase, particularly in the active medication arm, and lower doses were required given intolerable side effects including dry mouth, intoxication, and hypotension, most consistent with adverse effects from lofexidine. Surprisingly, the combination treatment was not more effective than placebo for promoting abstinence, reducing withdrawal symptoms, or retaining individuals in treatment. Some key differences between the lab study and the clinic setting included (1) tolerance to the medication and dosing, (2) duration of medication treatment, (3) inpatient vs outpatient setting, and (4) relapse prevention vs abstinence initiation design, all of which likely factored into the differences in the studies' outcomes.

The mostly negative results of dronabinol in the treatment of CUD likely have to do with its poor bioavailability [3], in conjunction with the differences in study designs. Dronabinol has a slow onset and long duration of action that can decrease craving and symptoms of withdrawal at doses that should produce minimal intoxication, thereby giving it a role in this specific component of treatment. However, its mixed effects on attenuating subjective effects and inability to impact reductions or abstinence rates in the clinic setting suggest it may be sufficient as a monotherapy or in combination with lofexidine in the treatment of CUD.

Given the issues with dronabinol, research has pursued other agonist formulations with better medication profiles as potential treatments for CUD. Nabilone, a DEA Schedule II (dronabinol is Schedule III) potent synthetic cannabinoid, is

currently FDA approved up to 6 mg per day for the second-line treatment of nausea and vomiting related to cancer chemotherapy treatment. It has better oral bioavailability, improved efficacy, and a more linear dose effect than dronabinol [3]. Because it is a synthetic cannabinoid and not naturally derived oral THC, unlike dronabinol, it has distinct urinary metabolites allowing for monitoring with urine cannabinoid testing as usual. This has the added benefit particularly in the real-world treatment setting of allowing for objective confirmation of patient self-report. To date, two human laboratory studies using nabilone, one as a monotherapy and one in combination with zolpidem, have demonstrated encouraging results for its role in the treatment of CUD. No clinical treatment trials to date have investigated nabilone for the treatment of CUD.

Haney et al. [8] looked at dose effects of nabilone and compared it to placebo in the human lab setting to assess its impact on cannabis withdrawal and relapse [8]. The study found that both doses of nabilone (6 mg and 8 mg) significantly decreased cannabis self-administration as a model of relapse, in addition to reducing ratings of irritability and "bad effect" during precipitated abstinence. High-dose nabilone (8 mg) also decreased craving. Nabilone reversed abstinence-induced sleep disturbances and changes to food intake. Placebo was associated with better performance on the cognitive tasks during abstinence. This study demonstrated that nabilone significantly reversed characteristic and problematic symptoms of cannabis withdrawal in addition to decreasing a model of relapse, by not only decreasing cannabis self-administration but reducing the use of cannabis in those who had relapsed from their baseline use. While there is a theoretical risk of abuse that is greater with nabilone than oral THC, at least in this study, participants reported few subjective effects from nabilone. It is likely that nabilone's properties as long acting and slow onset of action agonist may make it less likely to have the abuse liability of smoked cannabis. Overall, nabilone shows promise as a medication treatment in the prevention of relapse, particularly using the lens of harm reduction. The authors concluded that further research of nabilone for the treatment of CUD is needed in the clinic setting and in the context of abstinence initiation.

Given the positive lab findings of nabilone and a separate positive study of zolpidem for sleep disturbances related to cannabis cessation [25], a combination of the two medications was evaluated in the human lab as compared to zolpidem monotherapy [15]. In this study, heavy cannabis users were evaluated for their experience of cannabis withdrawal symptoms and relapse. The study found that while both medication exposures (nabilone 6 mg and zolpidem 12.5 mg) decreased withdrawal related sleep disturbances, only the combination attenuated withdrawal-related mood and food changes in addition to decreasing self-administration of active cannabis. While neither medication treatment changed cognitive performance, the combination medication did produce modest increases in abuse-related subjective ratings of capsules. It can be surmised from this second lab study that nabilone drove the decreases in self-administration and should be evaluated in clinical treatment trials for CUD. One limitation of the study was the fourth treatment arm of nabilone monotherapy was not included for comparison.

A recent randomized, placebo-controlled pilot study of nabilone (2 mg/day) for the treatment of CUD was completed in an outpatient treatment setting [16]. The study found no difference between nabilone and placebo in reducing self-report of cannabis use or urine cannabinoid levels. Most notably, the authors identify the limitations put on the maximum allowed dose by the FDA investigational drug application process as a likely factor in the negative trial findings, which is significantly lower (one third the dose) as compared to the human laboratory studies of nabilone using 6 mg [8, 25] to 8 mg [8].

A final agonist formulation of nabiximols has been investigated for its role in the treatment of cannabis withdrawal and CUD. Nabiximols contains extracts from the *Cannabis sativa* plant. These include THC, which would provide the agonist action, and cannabidiol (CBD), a cannabinoid with proposed effects on attenuating paranoia, euphoria, anxiety, and depression [27]. It has been proposed that CBD may also attenuate the euphoric effects of smoked THC and reduce intoxication [21]; thus it also has been investigated as a potential treatment for CUD and is presented in more detail in a separate chapter in this book. Notably, CBD has a varied and complex mechanism of action, with no direct effects at CB-1 receptors [27]. Given the interest in CBD and its potential therapeutic benefit, Haney et al. [11] completed a human lab study to assess the influence of a range of single doses of CBD on the reinforcing, subjective, cognitive, and physiological effects of smoked cannabis as compared to placebo during eight outpatient sessions. In this systematic study, the authors found that acute oral CBD pretreatment did not alter subjective, reinforcing, or cardiovascular effects of smoked cannabis in heavy cannabis users [11]. While they did not study chronic administration nor the same route of administration as the nabiximols study (oral vs buccal), both of which may have important implications for the impact of medication treatment [12], the investigators concluded that oral CBD likely does not have a role as a potential medication treatment for CUD. More information about CBD is provided in the chapter by García-Gutiérrez in this book.

In nabiximols, THC and CBD are in a 1:1 ratio that is administered through buccal spray that provides a more rapid onset of action and more favorable pharmacokinetics as compared to oral THC [27]. Allsop et al. [1] looked at nabiximols during an inpatient admission followed by a 28-day period without medication. The study found that nabiximols

significantly reduced the overall severity of cannabis withdrawal compared to placebo during the inpatient admission, including reductions in symptoms of irritability, depression, and craving, with limited but positive improvements in sleep, anxiety, appetite, physical symptoms, and restlessness. Nabiximols further reduced the time course of withdrawal symptoms during the inpatient admission by almost 2 days [1]. Patients receiving nabiximols stayed in inpatient treatment longer (better treatment retention), reported no greater intoxication, could not distinguish nabiximols from placebo spray, and had no difference in the number or type of adverse events. Though there were no differences in time to relapse after discharge from the inpatient setting, both groups reported reduced use of cannabis as confirmed with urine cannabinoid testing at follow-up, suggesting that inpatient treatment may be a stimulus for reduced use. Alternatively, inpatient treatment for CUD may also select for the most change-oriented and motivated patients. Given the positive impact on withdrawal but the lack of maintenance of nabiximols treatment, a follow-up trial is now underway. It is not surprising that acute detoxification without maintenance medication treatment did not lead to differences in abstinence, reductions in cannabis use, or time to relapse following discharge, as this is consistent with other acute substance abuse treatment episodes without continued care. A recent open-label outpatient case series demonstrated good tolerability of nabiximols in addition to reductions in cannabis use, craving, and withdrawal, warranting further exploration of nabiximols in the treatment of CUD [23, 24]. Since the added benefit of CBD is debatable [11], future trials should also do a direct comparison of nabiximols to another agonist, such as nabilone or oral THC, and if possible, by same route of administration (buccal).

CB-1 Receptor Antagonists

Human lab studies of both a single high dose (90 mg) of rimonabant [18] and repeated lower doses (40 mg) demonstrated reduced physiological and subjective effects of smoked cannabis [17]. This data would have provided the necessary early evidence to move forward from the human laboratory studies to the clinical treatment trial setting. However, rimonabant was found to also produce serious adverse psychiatric effects including anxiety, depression, and suicidality leading to the discontinuation of its use in clinical trials in the United States and precluded further investigation into the feasibility of its role in the treatment of CUD [22]. It is speculated that rimonabant's inverse agonist properties may be responsible for these adverse effects and that development of a neutral antagonist may be a promising treatment in CUD [2]. Preclinical studies are currently evaluating potential neutral CB-1 receptor antagonist agents [7], and those with promising preclinical findings and evidence of safety should be investigated in future clinical research.

Conclusion

In summary, medications with CB-1 receptor agonism are effective in treating cannabis withdrawal. CB-1 receptor agonists' role in the overall treatment of CUD is yet to be determined. Promising human laboratory work with nabilone and recent evidence of nabiximols in the inpatient treatment setting warrant further investigation into their usage in initiating abstinence or reductions in cannabis use in the outpatient treatment setting in addition to how maintenance treatment following inpatient detoxification may further prevent relapse. The only available CB-1 receptor antagonist investigated to date had significant serious adverse psychiatric effects that led to its discontinuation, despite previous positive human laboratory studies for its potential role in the treatment of CUD. CB-1 receptor antagonists with a more favorable side effect profile are in preclinical testing stages [7], and promising agents may have a role in the treatment of CUD.

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Neurotransmitter and Neuropeptide Targets for Cannabis Use Disorder Treatment

20

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Introduction

Although a high demand for effective interventions exists, few specific treatments have been developed for cannabis use disorders. Further, the treatments that have been examined have had limited efficacy, with few individuals achieving abstinence [31, 41, 51]. Recently, numerous studies have evaluated potential pharmacological interventions modulating specific neurotransmitters or neuropeptides believed to play a role in cannabis-related addictive processes. This chapter will focus on clinical trials that have investigated these targets as potential treatments for cannabis use disorders.

Serotonin

Serotonin has been implicated in a variety of neuropsychiatric behaviors and disorders including mood, anxiety, depression, appetite, sexual functioning, cognition, substance abuse, and response to antidepressants and antipsychotics. A growing body of evidence implicates cannabinoid interactions with the serotonin system. Cannabidiol (CBD), a major component of cannabis, has been shown to be a modest affinity agonist at the 5-HT1A receptor [35], and the anxiolytic and antidepressant effects of cannabidiol have been demonstrated to be mediated by 5-HT1A receptors [11, 56]. Low doses of the cannabinoid agonist WIN55,212-2 enhance 5-HT neurotransmission via cannabinoid receptor activation in the ventromedial prefrontal cortex and elicit potent antidepressant-like properties [3]. Further, work suggests that fluoxetine, a serotonin reuptake inhibitor, modulates CB1 receptor-mediated inhibition of adenyl cyclase through 5-HT1A receptor-dependent mechanisms [24].

In addition, agents targeting serotonin have demonstrated clinical utility in the treatment of anxiety and depression, conditions that often co-occur with cannabis use disorder. Data from the most recent National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III, 2012–2013) found that adults with recent or lifetime DSM-5 CUD were three times more likely to be diagnosed with an anxiety disorder and two-and-a-half to three times more likely to be diagnosed with major depressive disorder (MDD) than adults without CUD [13]. Moreover, there is a positive association between CUD severity and odds of having an anxiety or depressive disorder. As CUD severity increases (mild, moderate, severe), the odds of having a comorbid anxiety disorder or MDD increases (Anx: 2.2, 2.9, 4.4; MDD: 2.2, 3.1, 4.2; respectively), suggesting that those who may benefit most from pharmacotherapy are at greater risk for comorbidity. Clinical samples also show high comorbidity between CUD and anxiety and depressive disorders. In a baseline analysis from a multisite randomized clinical trial for CUD ($N = 302$), the most common psychiatric comorbidities were MDD (19.9%) and agoraphobia (15.2%) [42].

Anxious and depressive symptomology is also common in cannabis withdrawal syndrome, which has been a target of pharmacotherapy trials. Cannabis withdrawal is now well established [1, 5, 10] and reported by approximately one-third of regular cannabis users in the general population and up to 50–95% of heavy users in research studies (see [12], for review). Cannabis withdrawal is characterized by the following symptoms: irritability, anger, or aggression; nervousness or anxiety; sleep difficulty; changes in appetite; restlessness; depressed mood; and somatic complaints (e.g., headaches, chills, gastrointestinal discomfort). There is considerable overlap between anxiety and depressive disorders, cannabis withdrawal, and CUD, strongly implicating serotonin as a shared causal component and, thus, therapeutic

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target. However, clinical investigations of the utility of serotonergic medications for treatment of cannabis dependence have had largely mixed results.

Selective Serotonin Reuptake Inhibitors

The potential utility of serotonin reuptake inhibitors (SSRIs) for cannabis use was initially suggested by a secondary analysis in which fluoxetine significantly reduced cannabis use in depressed, adult alcohol-dependent individuals [8]. In a subsample of 22 comorbid cannabis users out of a total of 51 depressed alcohol-dependent individuals randomized to receive either fluoxetine or placebo, participants receiving placebo used almost 20 times as many cumulative cannabis cigarettes as compared to participants in the fluoxetine group. Further, the number of days of cannabis use during the study was five times higher in the placebo group than the fluoxetine group. However, a trial in adolescents and young adults with comorbid major depression and cannabis use disorders did not find a significant effect of fluoxetine on cannabis-related outcome measures [7]; lack of effect may have been attributable to the strong psychosocial platform used (cognitive behavioral therapy plus motivational enhancement therapy) as there were significant improvements in both depressive and cannabis symptoms in both the placebo- and fluoxetine-treated groups.

Subsequent trials evaluating SSRI efficacy for cannabis use in adult populations have also not had promising results. An evaluation of the SSRI escitalopram combined with cognitive behavioral and motivational enhancement therapy failed to find a positive effect of treatment on abstinence or withdrawal outcomes in 52 cannabis-dependent adults [54]. Vilazodone, an agent that combines the antidepressant activity of serotonin reuptake inhibition with partial agonist activity for 5-HT1A, was also studied in 76 cannabis-dependent individuals and was not more efficacious than placebo in reducing cannabis use [25]. Although both of these trials had significant attrition which could limit data interpretation, findings suggest that SSRIs have limited utility for treatment of cannabis use disorders other than potentially for comorbid conditions.

Buspirone

Buspirone, a partial 5-HT1A agonist, is a nonbenzodiazepine anxiolytic that has little or no abuse potential [18]. As discussed above, 5-HT1A activity appears to be altered in chronic cannabis use, and anxiety is a symptom of cannabis withdrawal, suggesting buspirone could be a potential medication candidate for treatment of cannabis use disorders. An initial pilot investigation of buspirone reduced percentage of positive urine drug screens among treatment completers, and a trend was observed for a lower percentage of positive drug screens in the entire sample [28]. However, a larger follow-up study (N = 175) did not find a medication effect on cannabis use outcomes and reported worse outcomes with buspirone treatment in women [26].

Dopamine

Dopamine is thought to play a key role in the reinforcing actions of drugs of abuse. In particular, an elevation of dopamine in mesolimbic pathways has been demonstrated with the administration of addictive drugs, including cannabis, and long-term administration of cannabis is associated with blunting of the dopamine system [4, 9, 47].

To date, limited work has investigated dopamine specifically as a treatment target for cannabis use disorder. Catechol-O-methyltransferase (COMT) inactivates catecholamine neurotransmitters and thus regulates levels of dopamine in the synapse. The COMT inhibitor entacapone was evaluated in an open-label trial of 36 patients with DSM-IV cannabis dependence. Entacapone (up to 2000 mg/day for 12 weeks) significantly decreased craving for cannabis in 52.7% of the patients; however, no data on cannabis use was reported, and a follow-up controlled trial has not been published [39]. Stimulant medications used for the treatment of attention-deficit/hyperactivity disorder (ADHD), such as methylphenidate and amphetamines, increase levels of dopamine in the central nervous system. Secondary analyses from investigations in other dependencies have shown some improvement in cannabis use with stimulant treatment. In individuals with methamphetamine use disorder, methylphenidate-SR treatment as compared to placebo was associated with fewer positive cannabis urine drug screens during the later portion of the trial [22]. A recent study involving individuals with co-occurring ADHD and cocaine dependence found that treatment with extended-release mixed-amphetamine salts resulted in a decrease in the proportion of participants using cannabis over time; however, a difference in proportion of cannabis use days over time was not observed [32].

Norepinephrine

The noradrenergic system has been implicated in the withdrawal/abstinence, stress, and craving aspects of drug dependence [2, 53]. As such, agents targeting norepinephrine have been evaluated as potential treatments for multiple dependencies, including cannabis. Given the overlap of nicotine and cannabis withdrawal symptoms, bupropion, an FDA-approved medication for tobacco smoking cessation was assessed as a potential treatment for cannabis use disorder. Bupropion inhibits the reuptake of norepinephrine and dopa-

mine and has some limited serotonergic activity. In a 13-week outpatient trial with cannabis-dependent adults, sustained-release bupropion was compared to the dual serotonin-norepinephrine reuptake inhibitor nefazodone and placebo; no change in cannabis use severity or cannabis withdrawal symptoms was observed with either treatment arm as compared to placebo [6]. More promising findings were reported in a preliminary outpatient study that utilized a paradigm similar to cigarette smoking cessation guidelines [34]. In this study, withdrawal symptoms were greater in the placebo-treated participants, and cannabis craving increased in participants receiving placebo but not in those receiving bupropion. However, a small number of participants completed the trial and were included in analyses ($n = 9$), significantly limiting data interpretation.

Atomoxetine, an FDA-approved medication for the treatment of attention-deficit/hyperactivity disorder (ADHD), has also been evaluated as a treatment for cannabis use disorder. By inhibiting reuptake of norepinephrine, atomoxetine increases levels of both dopamine and norepinephrine in the prefrontal cortex, but does not appear to increase dopamine in subcortical areas where there are few noradrenergic nerve terminals [44]. An open-label study of atomoxetine reported a trend toward reduction in cannabis use on self-report; however, this finding was not supported with urine drug screen results [48]. Further, adverse events were commonly reported, with 77% of subjects experiencing mild to moderate gastrointestinal side effects. A subsequent evaluation of atomoxetine combined with motivational enhancement therapy on the symptoms of ADHD and cannabis use in cannabis-dependent adults found greater improvement in some ADHD measurements, but not on cannabis use outcomes [29]. These results, taken together with the previous atomoxetine study, suggest that atomoxetine does not reduce cannabis use.

The dual serotonin-norepinephrine reuptake inhibitor venlafaxine has also been evaluated as a potential treatment for cannabis use disorder. Levin and colleagues examined the utility of the extended-release venlafaxine combined with cognitive behavioral therapy for co-occurring cannabis dependence and major depressive disorder or dysthymia [19], with the rationale that improving depressive symptoms would reduce cannabis use. However, venlafaxine was not better than placebo in reducing depressive symptoms. Further, participants receiving venlafaxine were less likely to reduce their cannabis use or become abstinent than participants receiving placebo. A secondary data analysis reported more severe withdrawal symptoms in the venlafaxine-treated group [16], raising the possibility that continued cannabis use may have been due to adverse effects of venlafaxine that overlap with cannabis withdrawal syndrome. Overall, studies suggest that noradrenergic agents are not promising compounds for the treatment of cannabis use disorders. Further, in some patients, noradrenergic agents may worsen outcomes.

Oxytocin

Hypothalamic neuropeptides are critical for integrating pleasurable and noxious somatosensory stimuli. In humans and rodents, oxytocin is released in response to touch, gentle vibration, and warmth [46, 49]. Noxious stimuli such as a forced swim test and immobilization have also been shown to promote oxytocin release in rodents, indicating that oxytocin is a multidimensional neuropeptide [15, 55]. Regulation of oxytocin release occurs within hypothalamic magnocellular neurons projecting to the posterior pituitary and parvocellular neurons projecting to the brain stem, spinal cord, and limbic nuclei. Peripherally, oxytocin elicits physiologic events necessary for copulation, parturition, and lactation [23]. Central release of oxytocin within the limbic nuclei has been implicated in "pro-social" behaviors, notably in response to stressful stimuli. Of interest, accumulating evidence also suggests that the endocannabinoid system plays a critical role in regulating stress response (see [14], for review), and recent work has demonstrated that endocannabinoid signaling is a mediator of oxytocin social reward [52].

As discussed above, virtually all drugs of abuse increase dopamine release in the nucleus accumbens. Molecular studies have localized oxytocin receptors to the mesolimbic dopamine reward circuit, including the amygdala, nucleus accumbens, ventral tegmental area (VTA), hippocampus, and ventral pallidum [50]. Interestingly, oxytocin infusion directly into the VTA promotes dopamine release in the nucleus accumbens, and systemic oxytocin administration promotes conditioned place preference in rodents, indicating that oxytocin is rewarding and necessary for mediating the salience of natural rewards [20, 30]. Earlier studies have indicated that drugs of abuse may encroach upon natural reward pathways. Behavioral studies utilizing animal models of drug reinforcement demonstrate that oxytocin dose dependently decreases cocaine-induced hyperactivity and stereotypy [36–38]. As chronic administration of oxytocin reduces dopamine release in the nucleus accumbens, oxytocin may be involved in the plasticity that occurs within the reward circuit as a function of repeated drug use [17]. However, studies of oxytocin and the long-term behavioral consequences of cocaine administration are conflicting. For example, oxytocin has been shown to facilitate cocaine-induced behavioral sensitization [38]. In a similar study, oxytocin inhibited the development of tolerance following repeated cocaine administration [37]. These disparate behavioral responses to oxytocin are likely dose related and possibly attributed to route of administration [17]. Immunohistochemical analysis of postmortem brains from alcohol-dependent individuals shows a significant reduction in oxytocin immunoreactivity in the hypothalamus [43], and mothers using cocaine during pregnancy exhibit significantly lower plasma oxytocin levels, as well as greater hostility and

depression than control mothers [21]. Small clinical trials have reported reductions in alcohol withdrawal [33] and cocaine craving [45] with short-term twice-daily oxytocin administration.

Two small, preliminary studies have been conducted examining the effect of oxytocin administration in cannabis using individuals. In the first study, cannabis-dependent adults who received 40 IUs intranasal oxytocin (n = 8) showed attenuated endocrine (DHEA) and subjective (self-reported craving) reactivity to the Trier Social Stress Test compared to placebo controls (n = 8) [27]. In a subsequent 4-week randomized pilot trial, oxytocin pretreatment immediately prior to motivational enhancement therapy engendered reduced cannabis sessions per day and amount used per day, while the placebo pretreatment group showed no significant reductions [40, 42]. Further investigation into the efficacy of oxytocin in reducing stress reactivity and enhancing motivational interventions in individuals with cannabis use disorder is needed.

Conclusion

Although preclinical data supports the rationale for targeting specific neurotransmitters to reduce cannabis use, outcomes from clinical trials have been somewhat disappointing. Serotonergic and noradrenergic agents have largely been shown to have limited value in the treatment of cannabis use disorders, showing some potential for comorbid substance use or psychiatric disorders. Limited work has also been conducted utilizing dopaminergic agents in this population, with resultant scant results. The neuropeptide oxytocin may have some promise as a therapeutic intervention for cannabis use; however, to date only preliminary data has been published, and no trials have yet been conducted in treatment-seeking individuals. More work is needed to identify effective pharmacotherapeutic interventions for cannabis use disorder.

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Anticonvulsants to Treat Cannabis Use Disorder

21

Barbara J. Mason

Introduction

Cannabis is the most widely used illicit drug in the world [52]. Patients seeking treatment for primary cannabis use disorder represent 25% of all substance use admissions globally [52]. Despite the widespread prevalence of the disorder and the numbers of individuals seeking treatment for it, there are no medications approved by the US Food and Drug Administration (FDA) for the treatment of cannabis use disorder and cannabis withdrawal.

The *Diagnostic and Statistical Manual of Mental Disorders* 5th Edition (DSM-V) [4] criteria for cannabis use disorder specify that at least 2 of 11 possible symptoms are present; symptoms include compulsive cannabis use despite negative consequences and craving for cannabis and the emergence of a withdrawal syndrome when cannabis use is discontinued. Cannabis withdrawal is present when three or more of seven possible symptoms develop after markedly cutting down or quitting heavy or prolonged cannabis use: irritability, anger or aggression, nervousness or anxiety, sleep difficulty (e.g., insomnia, disturbing dreams), decreased appetite or weight loss, restlessness, depressed mood, and somatic withdrawal symptoms [4]. Behavioral therapies currently comprise the main treatment approach for cannabis use disorder. However, behavioral therapies do not treat symptoms of cannabis withdrawal that may motivate a return to cannabis use. In addition, heavy cannabis use and withdrawal impairs executive functioning, creating a vulnerability to fail to inhibit maladaptive behaviors which may be associated with relapse to use and that may interfere with participation in cognitive therapies designed to promote and maintain abstinence. There is a general consensus that the agonist, antagonist, and antidepressant medication strategies typically applied in drug dependence have not demonstrated efficacy for reducing cannabis use in patients with cannabis use disorder in controlled clinical trials [20, 30, 34, 49, 54].

Anticonvulsants comprise a diverse group of drugs that are used to treat epileptic seizures and often bipolar disorder, neuropathic pain, and migraine. Antiepileptic drugs typically enhance γ-aminobutyric acid (GABA) function and block sodium (Na+) or calcium channels, which in turn reduces the release of excitatory glutamate. Through this neuromodulating mechanism of action, it is hypothesized that anticonvulsants will generally act to restore homeostasis in central inhibitory (GABA) and excitatory (glutamate) systems that become dysregulated in chronic heavy cannabis use and withdrawal [29].

A cannabis withdrawal syndrome characterized by an aggregate of superficially mild symptoms may be particularly responsive to treatment with an anticonvulsant. Specific anticonvulsants have been shown to have off-label effects that are relevant for the treatment of specific symptoms of cannabis withdrawal. For example, divalproex has been shown to reduce symptoms of irritability, aggression, and anger, and gabapentin is associated with reductions in sleep and mood disturbance across a range of disorders [38]. Topiramate and gabapentin have each shown efficacy for reducing alcohol use in patients with alcohol use disorder [5]. Thus, anticonvulsant drugs may offer a novel pharmacological treatment strategy, relative to the agonist, antagonist, or antidepressant approaches explored to date in cannabis use disorder. As such, they are not hypothesized to replace or block cannabis use, but to treat cannabis use disorder by normalizing emotional systems that become dysregulated through excessive cannabis use and discontinuation and which are hypothesized to continue to drive excessive use until emotional and motivational homeostasis is restored.

Anticonvulsants are generally viewed as safe when the recommended dose and medical contraindications and cautions on the product label are adhered to. Antiepileptic drugs as a group are associated with a risk of suicidal thoughts or behavior in about 1 in 500 patients taking these drugs for any indication. Abrupt withdrawal from anticonvulsants has

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Table 21.1 Double-blind, placebo-controlled studies of anticonvulsants for the treatment of cannabis use disorder

Drug (Study)	Patient characteristics	Treatment dose/ duration	Withdrawal symptoms	Cannabis consumption	Consequences
Divalproex [31]	*N* = 25 Age = 32.6 ± 5.8 years Male = 92% Cannabis dependent	Outpatient 1673 ± 344 mg/d Crossover: 6 × 6 weeks	Non-significant Craving visual analogue scale Snaith's irritability scale	Non-significant Self-report Urine toxicology	Non-significant Addiction Severity Index
Divalproex [21]	*N* = 7 Age = 26 ± 1 years Male = 85.7% Cannabis dependent	Outpatient/ inpatient 1500 mg/d Crossover: 29 × 29 days	↓ craving ↑ anxious, irritable, edgy, sleepy, withdrawn, yawning, disturbed sleep	Not measured	Not measured
Gabapentin [36]	*N* = 50 Age = 33.9 ± 9.7 years Male = 88% Cannabis dependent	Outpatient 1200 mg/d 12 weeks	↓ Marijuana Withdrawal Checklist ↓ craving ↓ Beck Depression Inventory II ↓ Pittsburgh Sleep Quality Index	↓ Timeline Followback interview ↓ urine toxicology	↓ Marijuana Problems Scale ↑ executive function
Topiramate [41]	*N* = 66 Age = 19.6 ± 2.1 years Male = 48% Cannabis users (abuse = 20.1%, dependence = 69.7%)	Outpatient 200 mg/d 6 weeks	↑ depression ↑ anxiety	Nonsignificant Timeline Followback interview Urine toxicology	↓ memory for words ↓ retrieval fluency ↓ attention, concentration ↑ reaction time ↑ confusion

precipitated seizures and status epilepticus; on and off titration is indicated. As with all centrally active medications, patients should be advised not to drive or operate heavy machinery until they have determined that the drug does not affect their performance.

The purpose of this chapter is to evaluate the efficacy and safety of anticonvulsants for the treatment of cannabis use disorder and withdrawal. A comprehensive literature search of PubMed and related databases was performed using multiple combinations of search terms to yield double-blind, placebo-controlled human laboratory and clinical studies assessing the therapeutic potential of anticonvulsants for cannabis use disorder and withdrawal. Reference lists of identified publications were searched for additional references, and clinicaltrials.gov was searched for posted results of clinical trials. The search yielded four completed prospective pilot studies, including one human laboratory study and three treatment studies; all were included in this review. The anticonvulsants evaluated for therapeutic potential in cannabis use disorder included divalproex sodium (Depakote and generics), gabapentin (Neurontin and generics), and topiramate (Topamax and generics). Included studies are summarized in Table 21.1.

All treatment studies included concomitant manualized behavioral therapy. Thus the comparison in treatment studies is behavioral therapy plus anticonvulsant medication relative to behavioral therapy plus placebo. Taken together, anticonvulsants may help restore normal brain functioning in patients with cannabis use disorder, reduce relapse risk, and decrease protracted symptoms of withdrawal, e.g., negative affect, insomnia and cannabis craving, thereby facilitating better engagement in behavioral treatment. Behavioral therapies in turn may enhance pharmacotherapy response by modifying attitudes and behaviors related to cannabis, increasing healthy life skills, and helping people to stay in treatment. The hypothesis is that combining anticonvulsant treatment with behavioral therapy will provide an incremental advantage in cannabis outcomes relative to the current standard of behavioral therapy alone.

Divalproex Background

Divalproex sodium (Depakote and generics) is an oral anticonvulsant drug that is indicated for the treatment of epilepsy and manic episodes associated with bipolar disorder and for the prophylaxis of migraine headaches [1]. The maximum recommended dose is 60 mg/kg/day for epilepsy and mania, and 1000 mg/day for migraines, to be taken in divided doses. The capacity of older patients (≥68 years of age) to eliminate drug is reduced compared to younger patients, and initial dosage should be reduced accordingly. A therapeutic plasma concentration is in the range of 50–125 μg/mL. Common side effects of divalproex include nausea, headache, sleepiness, vomiting, weakness, tremor, dizziness, stomach pain, blurry vision, double vision, diarrhea, increased appetite, weight gain, hair loss, loss of appetite, and problems with walking or coordination. Serious adverse reactions include hepatotoxic-

ity, pancreatitis, and fetal risk for neural tube defects and other major malformations (Pregnancy Category D).

The mechanisms by which divalproex and related compounds, valproic acid and sodium valproate, exert therapeutic effects for epilepsy, mania, and migraine have not been established. It has been suggested that efficacy may be related to increased brain concentration of GABA, inhibition of voltage-gated Na + channels, and indirect effects on non-GABAergic neurotransmission [47].

Divalproex has been used off-label to reduce symptoms of irritability, anger, and aggression. Early case studies reported improvement in rage attacks in an adult, agitation and aggression in diverse psychiatric patients, and explosive temper and mood lability in youth, with valproate or divalproex treatment [15, 18, 55]. These open-label findings were replicated by a double-blind, placebo-controlled trial of divalproex 750–1500 mg/d in 20 outpatients ages 10–18 years [15]. Patients met DSM-IV [3] criteria for oppositional defiant disorder or conduct disorder with chronic explosive temper and mood lability; six patients also met DSM-IV criteria for cannabis abuse. Patients were randomized to 6 weeks of double-blind treatment with divalproex or placebo and then crossed over for an additional 6 weeks of double-blind treatment with the alternate treatment. Divalproex was well-tolerated, and the mean drug plasma concentration of 82.2 ± 19.1 μg/mL indicated adequate dosing and medication adherence. Overall, 86% of those treated with divalproex met response criteria compared to 25% of placebo subjects. These data also lent preliminary support to the safety and therapeutic potential of divalproex in the subgroup of six patients with comorbid cannabis abuse.

Irritability, impulsivity, and aggressivity are commonly observed symptoms during withdrawal from a number of drugs. Two small open-label studies found valproate ($N = 4$) or divalproex ($N = 11$) reduced the intensity of symptoms of benzodiazepine withdrawal [8] and alcohol withdrawal [42]. Similarly, a series of case studies ($N = 20$) found divalproex ($\bar{x}$ dose = 1075 mg/d; $\bar{x}$ plasma valproate level = 58.5 μg/mL) to be safe and effective for the treatment of mood disorder with comorbid substance abuse in detoxified inpatients [2]. This cohort included a small subgroup of patients with cannabis abuse. Some patients spontaneously reported a reduction in craving with treatment, in addition to improvement in the targeted mood symptoms.

A 12-week double-blind placebo-controlled pilot study ($N = 29$) of divalproex (1500 mg/d) for alcohol relapse prevention did not find group differences on alcohol-related outcomes, but did find a significantly greater reduction in irritability, and a trend for greater decreases in lability and verbal assault, in patients treated with divalproex relative to placebo [10]. Divalproex was well-tolerated. A mean drug plasma concentration of 88.2 ± 20.1 μg/mL at Week 12 indicated adequate dosing and medication adherence.

Divalproex for the Treatment of Cannabis Use Disorder

Irritability, anger, and aggression are common symptoms of cannabis withdrawal and may precipitate relapse in cannabis use disorder. The literature reviewed above suggests that divalproex may be useful in diminishing these symptoms. As such, divalproex may also improve cannabis use outcomes. No safety concerns were raised in the subgroups of subjects with cannabis use disorder who were included in the studies reviewed above. Thus, a double-blind, placebo-controlled study ($N = 25$) of divalproex ($\bar{x}$ dose = 1673 ± 344 mg/d) was conducted for the treatment of cannabis use disorder ([31]; see Table 21.1). Outpatients were randomized to 6 weeks of double-blind treatment with divalproex or placebo and were then crossed over to an additional 6 weeks of double-blind treatment with the alternate treatment. All patients received concomitant weekly individual manualized relapse prevention behavioral therapy. Rates of abstinence were low, but both treatment groups showed a modest reduction in cannabis use, craving, and irritability over the course of the study. Divalproex showed no advantage over placebo on these study measures. Retention in treatment was high (>75%) in the first half of the study but decreased to about one-third in the latter half. Three patients treated with divalproex discontinued treatment due to complaints of jitteriness, depression, and/or abdominal cramping; one placebo patient was discontinued due to elevated bilirubin. Drug plasma concentration data suggested inconsistent medication adherence. The adverse events associated with treatment discontinuation (jitteriness, depression, abdominal cramping) overlap with symptoms of cannabis withdrawal. This adverse event profile, combined with the lack of positive effects on cannabis use measures, diminished enthusiasm for divalproex as a potential treatment for cannabis use disorder.

A randomized, placebo-controlled, double-blind, within-subject human laboratory study investigated the effects of 29 days of treatment with divalproex (1500 mg/d) relative to placebo, followed by a crossover to 29 days of the other treatment in 7 regular cannabis users ([21]; see Table 21.1). Dosing was supervised, and the last 2 weeks of each drug condition took place on an inpatient research unit, thus ensuring medication adherence which was subsequently verified by drug plasma concentration (78.2 ± 18.6 μg/mL). During abstinence, divalproex was associated with decreased craving and decreased visual analogue scale ratings of "content," "mellow," "social," "friendly," and "talkative" and increased ratings of "anxious," "irritable," "on edge," and "sleepy," relative to placebo. Under condition of cannabis administration, divalproex significantly increased ratings of "high" compared to placebo. Divalproex significantly worsened performance on numerous psychomotor tasks across both conditions of cannabis (abstinence and intoxication).

Divalproex was associated with significantly more subjective sleep complaints, as well as weight gain, relative to placebo. The unfavorable adverse drug effects obtained, particularly impaired psychomotor functioning, as well as symptoms similar to those associated with cannabis withdrawal such as anxiety, irritability, and disturbed sleep, in conjunction with limited evidence of efficacy, lend support to the earlier conclusion [31] that divalproex does not show promise as a potential pharmacotherapy for cannabis use disorder.

Gabapentin Background

Gabapentin (Neurontin and generics) is an oral medication that is FDA-approved for the treatment of epilepsy and postherpetic neuralgia. Approved dosing is up to 1800 mg/d, given in divided doses taken three times per day. Longer-acting proprietary formulations, gabapentin enacarbil (Horizant) and Gralise, are indicated for the treatment of postherpetic neuralgia; Horizant is also indicated for restless leg syndrome.

There are no contraindications to gabapentin, other than known hypersensitivity to the medication. Gabapentin is not metabolized in the liver. It is eliminated from systemic circulation by renal excretion as unchanged drug. A baseline test of creatinine clearance is indicated. Dose should be adjusted in patients with reduced renal function (creatinine clearance <60 mL/min). A lack of appreciable hepatic metabolism indicates gabapentin would not be expected to influence nor be influenced by cannabis use or concomitant medications through hepatic-mediated mechanisms [28, 44]. Gabapentin plasma levels are not associated with efficacy and are thus not obtained routinely. Based on significant clinical and post-marketing experience for approved pain and epilepsy indications, gabapentin is considered to have a good safety and tolerability profile. The most commonly reported adverse events with gabapentin in comparison to placebo-treated patients in pivotal trials include dizziness, somnolence, peripheral edema, ataxia, fatigue, and nystagmus. Warnings include drug reaction with eosinophilia and multiorgan sensitivity, anaphylaxis, and angioedema. Gabapentin is Pregnancy Category C.

Reports of abuse of gabapentinoids, such as gabapentin and pregabalin, are increasingly being documented in high-risk populations, notably opioid and prescription drug abusers. Gabapentin is not a controlled or scheduled substance. There was no evidence of tolerance to gabapentin dose, rebound with titration off drug, nor evidence of abuse potential in studies of alcohol dependence [38]. However, patients undergoing opioid withdrawal, those who misuse prescriptions recreationally, and prison populations may be at increased risk to misuse gabapentin, with self-administered doses often far exceeding the therapeutic range [13, 51]. Hence, patients with risk histories should be monitored for potential gabapentinoid misuse or diversion, e.g., self-dose escalation or a "need" for unusually high doses, repeated requests to replace "lost" medication, and other drug-seeking behaviors.

Gabapentin is used off-label for the treatment of alcohol use disorder [5, 38]. A number of double-blind, placebo-controlled single-site trials in patients with alcohol use disorder have found an association between gabapentin and decreased rates of drinking and heavy drinking and increased rates of abstinence [6, 7, 11, 16, 37]. Gabapentin has also been shown to improve symptoms of mild to moderate alcohol withdrawal (see [38] for review). Beneficial effects of gabapentin have been reported on measures of alcohol craving [16, 35, 37] and on measures of alcohol-related sleep disturbance and negative affect [6, 7, 26, 27, 35, 37]. Alcohol-gabapentin interaction studies found alcohol did not affect the pharmacokinetics of gabapentin, nor did gabapentin alter the intoxicating, subjective, and performance effects of alcohol, or induce alcohol craving or self-administration relative to placebo [9, 43]. Promising effects of gabapentin in decreasing cocaine and methamphetamine use in open-label studies were not replicated in subsequent double-blind placebo-controlled trials (see [38] for review).

Gabapentin for the Treatment of Cannabis Use Disorder

Gabapentin is believed to act by blocking a specific alpha-2d subunit of the voltage-gated calcium channel at selective presynaptic sites and, as a result, to indirectly modulate GABAergic mechanisms [50]. Preclinical findings suggest that gabapentin normalizes CRF-induced GABA activation in the amygdala [45, 46]. These GABA-CRF interactions and their role in the motivational aspects of cannabis relapse provide a preclinical rationale for exploring the efficacy of gabapentin in cannabis use disorder [33]. Furthermore, in clinical studies of various disorders, gabapentin has been found to reduce craving and disturbances in sleep and mood [6, 7, 17, 22, 26, 32, 35, 37, 38], which are among the most persistent symptoms of protracted cannabis withdrawal and a key reason patients resume using cannabis. A pattern of continued heavy cannabis use and withdrawal also has been found to alter right prefrontal brain activity and impair executive functions, such as inhibition of impulses, cognitive flexibility, and complex information processing [14, 19, 53]. These changes in brain function may make it difficult for patients to effectively use the components of standard behavioral therapies. Cannabis-related impairment in executive function, e.g., failure to inhibit impulses, also may contribute

to the high dropout rates (≈60%) typically found in non-agonist clinical trials of primary cannabis dependence [12, 31, 39, 40]. Gabapentin showed subtle cognitive-enhancing effects in the domains of attention, concentration, visual-motor functioning, inhibition, and set shifting in healthy volunteers [48]. Thus, gabapentin, through its calcium-channel-GABAergic mechanism of action that has relevance for restoring homeostasis in brain stress (CRF) systems, may offer a novel treatment approach for cannabis withdrawal and cannabis use disorder, and cognitive consequences of chronic heavy cannabis use.

A proof-of-concept pilot study evaluated the safety and efficacy of gabapentin 1200 mg/d for the treatment of cannabis dependence ([36]; see Table 21.1). This 12-week, randomized, double-blind, placebo-controlled clinical trial was conducted in 50 outpatients diagnosed with current cannabis dependence. Manual-guided, abstinence-oriented individual counseling was provided weekly to all participants. Relative to placebo, gabapentin significantly reduced cannabis use as measured both by urine toxicology ($p = 0.001$) and by the Timeline Followback interview ($p = 0.004$) and significantly decreased withdrawal symptoms as measured by the Marijuana Withdrawal Checklist ($p < 0.001$), Beck Depression Inventory II ($p = 0.009$), and Pittsburgh Sleep Quality Index ($p < 0.001$). Gabapentin was also associated with significantly greater improvement in overall performance on tests of executive function ($p = 0.029$). The improvement in executive function found with gabapentin may represent a direct effect of the drug [48] and/or an indirect effect gained by decreasing marijuana withdrawal and use.

A limitation of this pilot study was the relatively small number of subjects in each group and a high rapid dropout rate, making outcome assessments unavailable for 18% of the sample. An analysis of baseline predictors of dropout found that individuals' impaired ability to inhibit impulses and process complex information were significant predictors for leaving treatment, as were the age at first marijuana use, years of daily marijuana use, and marijuana withdrawal severity. The risk for premature treatment termination posed by these cognitive factors and cannabis dependence severity underscores the importance of developing safe and effective pharmacological treatments for reducing cannabis use and withdrawal severity and for optimizing cognitive executive function. Such pharmacological treatment may help patients take better advantage of behavioral therapy aimed at supporting recovery, as gabapentin combined with abstinence-oriented counseling resulted in outcomes superior to those of placebo combined with counseling. This pilot study provided preliminary support for the safety and efficacy of gabapentin for treatment of cannabis dependence that merits further study.

Topiramate Background

Topiramate (Topamax and generics) is an oral drug that is FDA-approved for the treatment of epilepsy and for the prophylaxis of migraine. The recommended dose is 100–400 mg/d in two divided doses for approved indications. While topiramate has no contraindications, it has a number of warnings and precautions. Warnings include risk of acute myopia and secondary angle closure glaucoma, decreased sweating and increased body temperature, kidney stones, hyperammonemia, and encephalopathy. Recommended lab tests include baseline and periodic measures of serum bicarbonate to detect treatment-emergent metabolic acidosis; baseline tests of renal function as creatinine clearance <70 mL/min requires a dose adjustment to half the starting and maintenance dose; and baseline tests of hepatic function, as topiramate plasma concentration is increased in hepatic impairment. Cognitive dysfunction is an adverse event commonly associated with treatment discontinuation, symptoms of which may include confusion, psychomotor slowing, attention, concentration and memory impairment, and speech or language problems (particularly word-finding difficulties) [48]. Other central nervous system adverse events include dizziness, somnolence, fatigue, depression, or mood problems. Topiramate interacts pharmacokinetically with some antiepileptic drugs, CNS depressants, oral contraceptives, metformin, lithium, and carbonic anhydrase inhibitors, with significant changes in drug plasma concentrations. Topiramate is Pregnancy Category D; infants exposed in utero have an increased risk of cleft lip and/or palate, particularly if exposure occurs in the first trimester (when many women do not know they are pregnant).

The mechanisms by which topiramate exerts therapeutic effects for epilepsy and migraines have not been established. It has been suggested that efficacy may be related to blockade of voltage-dependent Na + channels, augmentation of activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonism of the AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV [23].

Topiramate is also used off-label as a treatment for alcohol use disorder [5]. A recent meta-analysis of randomized controlled trials of ≥3-month duration and dose titration to a target dose of 200–300 mg/d in outpatients with alcohol use disorder found a weighted mean difference (WMD) for fewer drinking days (WMD, −6.5%; 95% CI, −12.0% to −1%), fewer heavy drinking days (WMD, −9%; 95% CI, −15.3% to −2.7%), and fewer drinks per drinking day (WMD, −1.0; 95% CI, −1.6 to −0.48) with topiramate relative to placebo treatment [25]. Corresponding analyses of numbers needed to harm (NNH) found patients treated with topiramate had a

higher risk of cognitive dysfunction (NNH, 12; 95% CI, 7 to 84), paresthesias (NNH, 4; 95% CI, 3 to 7), and taste abnormalities (NNH 7; 95% CI, 5 to 15) than did patients treated with placebo [25].

Topiramate for the Treatment of Cannabis Use Disorder

Cannabis use is disproportionately high among adolescents and young adults [24], but this population is typically excluded from clinical trials for cannabis use disorder. Given the association between topiramate and significant reductions in alcohol use in adults, the availability of topiramate for use in pediatric patients ≥2 years of age, and its effects on potentiation of GABA and antagonism of glutamate, it was hypothesized that topiramate would have therapeutic potential by reducing the acute reinforcing effects of cannabis in heavy cannabis users, ages 15–24 years [41].

A 6-week randomized, double-blind, placebo-controlled outpatient trial of topiramate (200 mg/d) was conducted in 66 heavy cannabis using youth (see Table 21.1). All patients received concomitant motivation enhancement therapy. Groups did not differ significantly on measures of quantity and frequency of cannabis use across the study, nor on rates of positive urine screens. Attrition was disproportionately high with topiramate treatment (52.5%) relative to placebo (23.1%). Two-thirds of those terminating topiramate did so due to adverse medication side effects, namely, depression, anxiety, difficulty with coordination or balance, weight loss, and paresthesias. Tests of neurocognitive performance showed decreased performance on retrieval fluency and memory for words with topiramate treatment relative to placebo. The overall lack of efficacy and poor tolerability of topiramate in this pilot study of cannabis misuse in youth reduces enthusiasm for this treatment. The increased cognitive impairments found with topiramate relative to placebo are a particular concern in a youthful population abusing cannabis, which by itself is associated with cognitive impairment and poor educational outcome [53].

Summary

Three anticonvulsants have been studied for the treatment of cannabis use disorder: divalproex, gabapentin, and topiramate. Drugs were selected for study based on off-label use in other substance use disorders (primarily alcohol use disorder) and because of reported benefits for various symptoms associated with cannabis withdrawal. For example, divalproex has been found to reduce symptoms of irritability, anger, and aggression, and gabapentin has been found to reduce disturbances in sleep and mood, across a range of disorders.

Studies were well-designed and used random assignment to double-blind, placebo-controlled treatment conditions. Oral dosing was within the approved therapeutic range, and adherence typically was verified by plasma concentration. Cannabis use was determined by both self-report and urine toxicology. Treatment studies provided concomitant behavioral therapy for all study participants.

Divalproex did not show efficacy for reducing cannabis use and withdrawal symptoms (craving, irritability) in a clinical trial involving 25 outpatients with cannabis dependence. Three patients discontinued divalproex due to adverse drug reactions of jitteriness, depression, and abdominal cramping [31]. A human laboratory study in seven non-treatment-seeking cannabis-using volunteers found a reduction in cannabis craving with divalproex relative to placebo but also found increased self-reports of anxiety, irritability, edginess, and sleepiness during cannabis abstinence [21]. Under conditions of cannabis administration, divalproex significantly increased self-reports of "high." Divalproex significantly worsened performance on numerous psychomotor tasks during both cannabis abstinence and self-administration. Overall, the unfavorable adverse drug reactions obtained with divalproex, in conjunction with limited evidence for efficacy, diminished enthusiasm for this anticonvulsant as a potential treatment for cannabis use disorder.

Gabapentin was associated with significantly decreased cannabis use relative to placebo, as measured by both urine toxicology and self-report, in a clinical trial involving 50 outpatients with cannabis dependence [36]. Gabapentin was associated with significant reductions in symptoms of cannabis withdrawal, including cannabis craving and disturbances in sleep and mood. A significant overall improvement in executive function was also associated with gabapentin relative to placebo. Gabapentin was well-tolerated, and adverse reactions did not differ from placebo. The beneficial effects of gabapentin on cannabis use and withdrawal measures, combined with a favorable safety and tolerability profile, support further evaluation of gabapentin as a treatment for cannabis use disorder and withdrawal.

Topiramate did not generally show efficacy for reducing cannabis use relative to placebo, either by self-report or urine toxicology, in a clinical trial involving 66 heavy cannabis using youth [41]. The attrition rate with topiramate was high and twice that of placebo, largely due to adverse drug reactions including depression, anxiety, decreased coordination, and neurocognitive test performance. Limited evidence of efficacy combined with poor tolerability diminish enthusiasm for topiramate as a new treatment for cannabis use disorder.

Discussion

The studies of anticonvulsants for the treatment of cannabis use disorder reviewed in this chapter were pilot studies and consequently relatively small in sample size. Studies also displayed the retention problems that tend to characterize non-agonist trials in a cannabis using population. Despite these limitations, the carefully controlled-research designs and well-considered study measures facilitated clear conclusions. Divalproex and topiramate showed little evidence of efficacy for cannabis use disorder and were poorly tolerated. Both drugs were associated with adverse drug reactions involving neurocognitive impairment, as also found in cannabis use per se. Both drugs also increased negative affect, which is also part of the motivational syndrome of cannabis withdrawal that is associated with relapse. Thus, the harms relative to the lack of efficacy do not support the use of divalproex and topiramate in the treatment of cannabis use disorder. Conversely, gabapentin showed an incremental benefit over placebo in decreasing cannabis use on urine toxicology and self-report measures and in decreasing withdrawal symptoms, including cannabis craving, negative affect, and sleep disturbance. These results, combined with good safety and tolerability in patients with cannabis dependence, support further evaluation of gabapentin as a treatment for cannabis use disorder and withdrawal.

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Prodrugs as Treatments for Cannabis Use Disorder: *N*-Acetylcysteine as a Case Example

22

Kevin M. Gray

Introduction

Prodrugs, precursor compounds that undergo in vivo transformation to pharmacologically active agents, offer advantages in drug development when the active compounds have limitations in stability or pharmacokinetics [27]. *N*-acetylcysteine (NAC), the *N*-acetyl prodrug of the amino acid cysteine, has been used clinically for several decades, most notably as an antidote to acetaminophen overdose and as a bronchomucolytic agent. More recently, NAC has been the subject of expanding interest as a potential therapeutic agent for an array of psychiatric and substance use disorders [3, 5, 22, 34]. NAC administration promotes synthesis of the endogenous antioxidant glutathione, and it affects glutamate homeostasis by promoting cystine-glutamate exchange and upregulating the astroglial glutamate transporter GLT-1 [28]. These antioxidant and glutamatergic mechanisms likely underlie NAC's central nervous system therapeutic applications. Interest in NAC is bolstered by its inexpensive over-the-counter availability and its established safety.

Investigation of NAC as a potential addiction pharmacotherapy is derived from preclinical work demonstrating the role of glutamate dysregulation in addiction neuropathology and drug-seeking behavior [14]. NAC was shown to reverse cocaine-induced metaplasticity and prevent relapse [26]. Similar findings emerged in nicotine [25] and opioid [36] animal models, indicating that NAC may have therapeutic application across a variety of substance use disorders.

In light of promising preclinical findings across multiple substances, as well as encouraging early work in humans with cocaine use disorder [17–19], our team became interested in potential application of NAC to CUD. Observing that cannabis use onset typically occurs during adolescence, that young adults are more likely to meet criteria for CUD than any other age group, and that most young people do not respond adequately to evidence-based treatments for CUD, we sought to establish proof of concept of a trial of NAC in young cannabis users [13, 35]. This work was designed to assess the feasibility of potential future trials of NAC to complement evidence-based psychosocial treatments in young people with CUD.

After obtaining United States Food and Drug Administration Investigational New Drug and Institutional Review Board approval, we undertook a 4-week open-label trial of NAC 1200 mg twice daily in young people ($N = 24$, ages 18–21) with CUD [12]. Participants expressed willingness to reduce cannabis use, but interest in cessation was not a requirement for enrollment.

At baseline and weekly during NAC treatment, participants self-reported cannabis use via Timeline Follow-Back methods, rated cannabis craving via the Marijuana Craving Questionnaire (MCQ), and submitted urine samples for semiquantitative cannabinoid testing (range 0–135 ng/mL). Pill counts and medication administration diaries were used to track medication adherence, and medical clinician assessments were used to monitor adverse events.

Goal enrollment occurred rapidly, and participants generally complied with study procedures, suggesting that this line of work could be feasibly conducted with this population. Pill counts and self-report diaries indicated that participants took 82.6% ± SE 2.6% of dispensed NAC doses. Adverse events were all deemed mild or moderate, and none led to medication discontinuation.

While the lack of a placebo comparison group limited the interpretability of findings associated with cannabis use, participants reported statistically significant reductions in cannabis use and MCQ-measured craving (overall MCQ score as well as three of four MCQ domain scores). The use of a semiquantitative urine cannabinoid test was a notable limitation, as 13 participants never submitted a urine specimen below the 135 ng/mL threshold.

Overall, this proof-of-concept trial indicated that trials of NAC could be feasibly conducted in young people with

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CUD. Coupled with preclinical and preliminary clinical work across other substances, the findings provided justification and rationale for more rigorous trials of NAC for CUD.

Adolescent Randomized Controlled Trial

Our team devised a randomized, placebo-controlled trial of NAC for CUD in adolescents, with the goal of optimizing design details based on signals from preclinical and preliminary clinical findings. An older adolescent age range (15–21 years old) was chosen in light of high prevalence of CUD, strong evidence of cannabis-related harms, and limited outcomes with current evidence-based treatments for CUD in this age group [13, 35]. The dose of NAC, 1200 mg twice daily, was chosen based on evidence of tolerability and possible signal of therapeutic benefit in prior preliminary trials among individuals with substance use disorders [12, 15, 17–19].

The embedded psychosocial treatment to be provided across randomization groups, brief weekly cessation counseling provided by a medical clinician, was chosen to optimize translation to real-world clinical practice settings. The behavioral treatment contingency management (CM) was added to this psychosocial approach for multiple reasons. First, given the consistent evidence that CM is a powerful adjunct to psychosocial treatment for youth cannabis cessation, maximizing response to psychosocial/behavioral interventions, this was seen as a strong platform for testing the potential role of NAC as an adjunctive pharmacotherapy [32, 33]. In other words, we sought to test NAC on the strongest possible platform, reasoning that if NAC provides additive benefit on this platform, then it may have a role across other potentially less powerful psychosocial and behavioral platforms. Second, our prior work had revealed potential synergy between CM and pharmacotherapy for adolescent tobacco cessation, with CM behaviorally reinforcing abstinence and pharmacotherapy reducing symptoms that maintain substance use [12]. We anticipated a possible similar pattern in a trial targeting youth CUD. Third, preclinical and preliminary clinical findings suggested that NAC may be best suited to relapse prevention in individuals who have achieved initial abstinence, and we reasoned that CM may provide the necessary behavioral reinforcement of early abstinence, providing an opportunity for NAC to exert its effects [8, 16]. We opted to utilize a two-tiered CM model, using escalating reinforcement with resets for both visit attendance and negative urine cannabinoid tests, based on prior work with young adults with CUD [4]. This model is well suited to CUD, given that heavy/frequent cannabis users may have positive urine cannabinoid tests for weeks after becoming abstinent. This model allows for early exposure to behavioral reinforcements even in light of potentially delayed reinforcement of abstinence.

With the aforementioned design features, we undertook an 8-week double-blind placebo-controlled trial of NAC 1200 mg twice daily, added to brief medical clinician-delivered cessation counseling and CM, for older adolescents (ages 15–21) with CUD [9]. The study, with a target sample size of $N = 116$ (58 receiving NAC and 58 receiving placebo), was powered to detect a 50% rate of negative urine cannabinoid tests in the NAC group, compared with 25% in the placebo group, based on estimates from a previous trial of pharmacotherapy to complement CM targeting cocaine dependence [24]. While the study included a posttreatment follow-up visit (on week 12), the trial was not powered to detect posttreatment abstinence outcomes. Urine cannabinoid levels were assessed at weekly clinical visits throughout treatment, and self-reported cannabis use was assessed via Timeline Follow-Back methods. The primary outcome was qualitative urine cannabinoid testing (positive versus negative, at cutoff of 50 ng/mL) during the 8 weeks of treatment, with efficacy evaluated by proportion of negative urine cannabinoid tests compared between NAC and placebo groups, via a repeated-measures logistic regression model using the methods of generalized estimating equations. For the purpose of intent-to-treat analysis, all missing urine tests were assumed to be positive. Secondary exploratory efficacy analyses incorporated various combinations of urine cannabinoid tests and self-reported cannabis use. Adverse events were assessed at weekly clinic visits by the medical clinician and evaluated for severity and relatedness to study procedures.

Of the 116 randomized participants, 106 (92%) took at least 1 dose of study medication, 70 (60%) were retained through completion of treatment, and 54 (47%) attended the posttreatment follow-up visit. Retention did not differ between groups. Medication adherence, measured via pill counts and review of medication diaries, revealed that 95% of dispensed NAC doses and 93% of dispensed placebo doses were taken. There were no United States Food and Drug Administration-defined serious adverse events, and there were no significant differences between NAC and placebo groups in the occurrence of any adverse events. Only one participant in the study discontinued medication due to an adverse event – this individual was in the NAC group and discontinued due to severe heartburn, which resolved with medication discontinuation.

Participants in the NAC group had more than double the odds of negative urine cannabinoid tests during treatment compared with those in the placebo group (odds ratio = 2.4, 95% confidence interval = 1.1–5.2; $\chi^2 = 4.72$, $p = 0.029$) (Fig. 22.1). Through the final treatment visit, 40.9% of the urine cannabinoid tests in the NAC group were negative, compared with 27.2% in the placebo group, in the intent-to-treat model in which missing urine tests were assumed to be

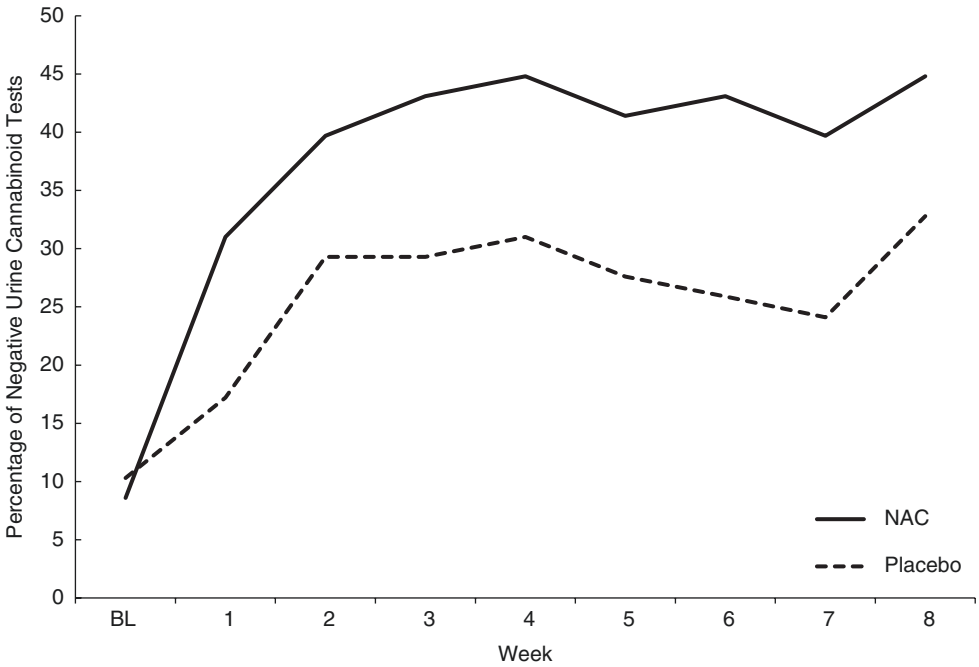

Fig. 22.1 Intent-to-treat urine cannabinoid test results in the adolescent trial

positive. Exploratory secondary analysis revealed that biologically confirmed self-reported abstinence during the final 2 weeks of treatment was achieved by 36.2% of NAC participants, compared to 20.7% of placebo participants (odds ratio = 2.32, 95% confidence interval = 0.99–5.43; $p = 0.054$). At the posttreatment follow-up visit, 19.0% of NAC participants and 10.3% of placebo participants had negative urine cannabinoid tests (odds ratio 2.4, 95% confidence interval 0.8–7.5; $\chi^2 = 2.2$, $p = 0.131$).

We sought to determine whether NAC's effect on cannabis abstinence may be mediated by craving, via evaluation of participant responses on the 12-item Marijuana Craving Questionnaire (MCQ) [29]. While overall statistically and clinically significant reductions in craving were observed over the course of treatment, there were no significant differences in MCQ trajectories between the NAC and placebo groups.

We then examined the potential role of impulsivity as a predictor of treatment response [2]. Participants self-rated impulsivity via the Barratt Impulsiveness Scale (BIS) prior to treatment. After median split of BIS ratings (dividing into high impulsivity (HI) and low impulsivity (LI) groups), it was noted that LI participants had double the odds of having negative urine cannabinoid tests during treatment compared with HI participants (odds ratio = 2.14, 95% confidence interval = 1.01–4.54; $\chi^2 = 3.9$, $p = 0.049$). While NAC appeared more efficacious in the LI group, there was not an impulsivity by treatment group interaction, indicating that NAC was efficacious in both LI and HI groups. Adherence to NAC, compared to nonadherence, was associated with more than four times the odds of negative urine cannabinoid tests (odds ratio = 4.49, 95% confidence interval = 1.24–16.23; $\chi^2 = 8.65$, $p = 0.022$), but adherence had no relationship with abstinence in the placebo group. While LI participants were more likely to be adherent with study medication than HI participants, adherence to NAC, compared to nonadherence, was particularly predictive of negative urine cannabinoid tests in the HI group (odds ratio = 8.08, 95% confidence interval = 1.43–45.70; $\chi^2 = 5.6$, $p = 0.018$). We concluded that efforts to optimize NAC adherence may be particularly critical for HI individuals.

We additionally sought to determine the influence of tobacco and alcohol co-use among participants in the trial. Being a cigarette smoker did not influence the effects of NAC on cannabis abstinence, and there was no significant increase or decrease in cigarettes per day in either NAC or placebo groups over the course of treatment [20]. While no compensatory increase in cigarette smoking was noted with cannabis cessation, study interventions did not yield an effect on cigarette reduction. There was similarly no compensatory increase in alcohol use during treatment. In fact, among NAC participants, lower levels of cannabis use were associated with less alcohol use, suggesting potential generalization of NAC effects across substances [30].

Adult Randomized Controlled Trial

In an effort to determine if NAC's efficacy extends from adolescents to adults, a multisite placebo-controlled trial was conducted within the National Drug Abuse Treatment

Clinical Trials Network. Design elements mirrored those in the prior adolescent randomized trial, with only minor adjustments [23]. The magnitude of CM reward for visit attendance was increased, as it was presumed a higher magnitude reinforcement may be necessary with adults than with adolescents. Active treatment was conducted for 12 weeks rather than 8 weeks, to provide more opportunity to detect treatment effects. A larger sample size (N = 300, ages 18–50) was planned in order to provide adequate power to detect end-of-treatment abstinence effects, though the primary efficacy analytic approach and outcome was the same as was used in the adolescent trial. The same dose of NAC (1200 mg twice daily) was used, but in the adult trial, a riboflavin biomarker was added to all medication capsules (25 mg per 600 mg capsules, yielding a total of 100 mg riboflavin per day).

A total of 302 participants were randomized, with 153 in the NAC group and 149 in the placebo group [11]. While 72% of NAC participants and 69% of placebo participants were retained through the end of treatment, only 31 NAC and 26 placebo participants met strict criteria for medication adherence (taking ≥80% of dispensed study medication per study week, confirmed by urine riboflavin biomarker testing). The adolescent trial did not incorporate riboflavin testing as a biomarker of adherence, so direct comparison of this finding is not possible. However, using parallel methods between trials (pill counts to confirm medication diaries), 73% of dispensed NAC doses and 72% of placebo doses were taken in the adult trial, compared with 95% and 93%, respectively, in the adolescent trial. Adverse effects were infrequent, without clinically significant between-group differences in rates of overall or specific events.

In contrast with the prior adolescent study, there was no statistically significant evidence that the NAC and placebo groups differed in cannabis abstinence (odds ratio = 1.00, 95% confidence interval = 0.63–1.59; p = 0.984) (Fig. 22.2). Overall, 22.3% of urine cannabinoid tests in the NAC group were negative, compared to 22.4% in the placebo group. Baseline tobacco smoking status was a strong indicator of cannabis outcomes, with tobacco smokers being half as likely as non-tobacco smokers to achieve cannabis abstinence during treatment (odds ratio = 0.52, 95% confidence interval = 0.31–0.88; p = 0.008). Hispanic/Latino participants were half as likely as non-Hispanic/Latino participants to test negative for cannabinoids during treatment (odds ratio = 0.52, 95% confidence interval = 0.27–1.00, p = 0.30), but there was no ethnicity-by-treatment interaction. There was a trend-level race-by-treatment interaction, suggesting that while racial minority participants had overall lower proportions of negative urine cannabinoid tests, they differentially responded more favorably to NAC than to placebo (white NAC versus placebo odds ratio = 0.81, 95% confidence interval = 0.46–4.63; racial minority NAC versus placebo odds ratio = 1.97, 95% confidence interval = 0.84–4.63; race-by-treatment interaction p = 0.083) (Fig. 22.3). White participants had higher placebo response rates than racial minority participants, possibly allowing NAC therapeutic effects (otherwise masked by higher placebo abstinence rates among white participants) to emerge among racial minority participants.

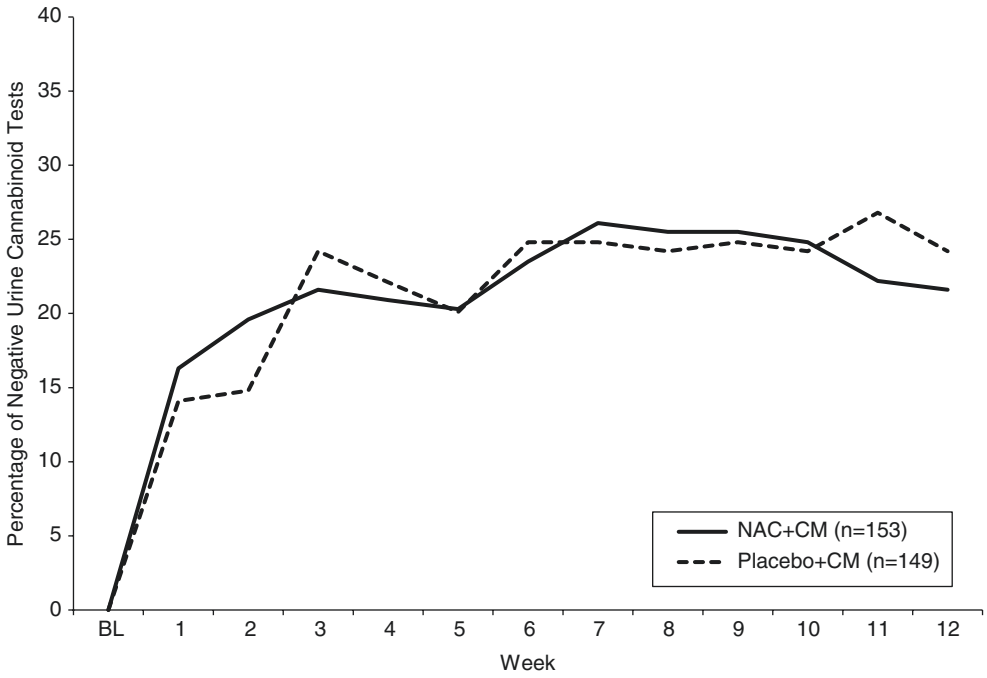

Fig. 22.2 Intent-to-treat urine cannabinoid test results in the adult trial

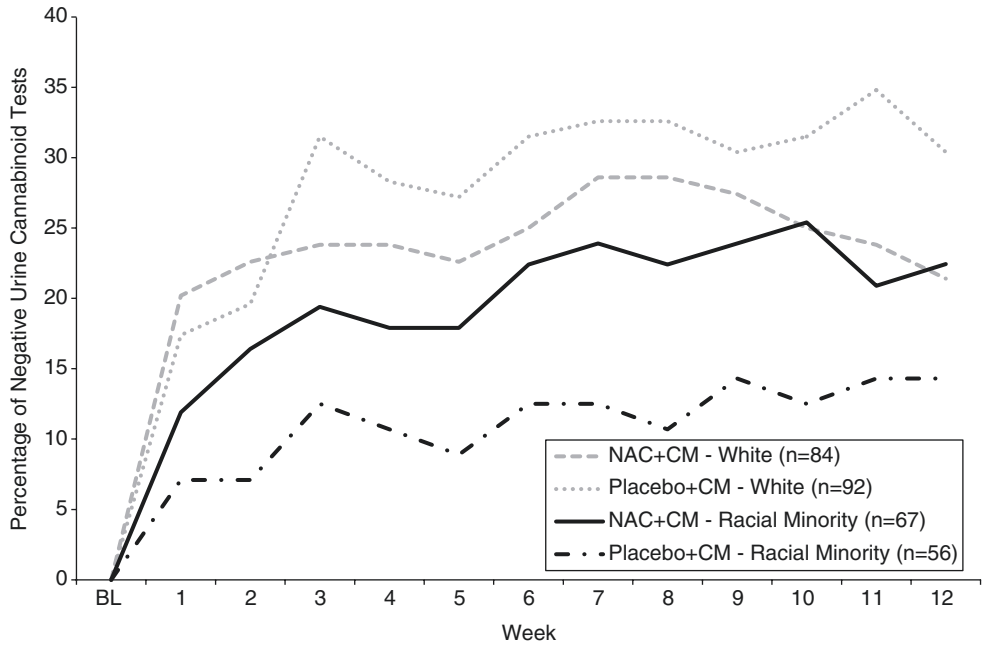

Fig. 22.3 Race and intent-to-treat urine cannabinoid test results in the adult trial

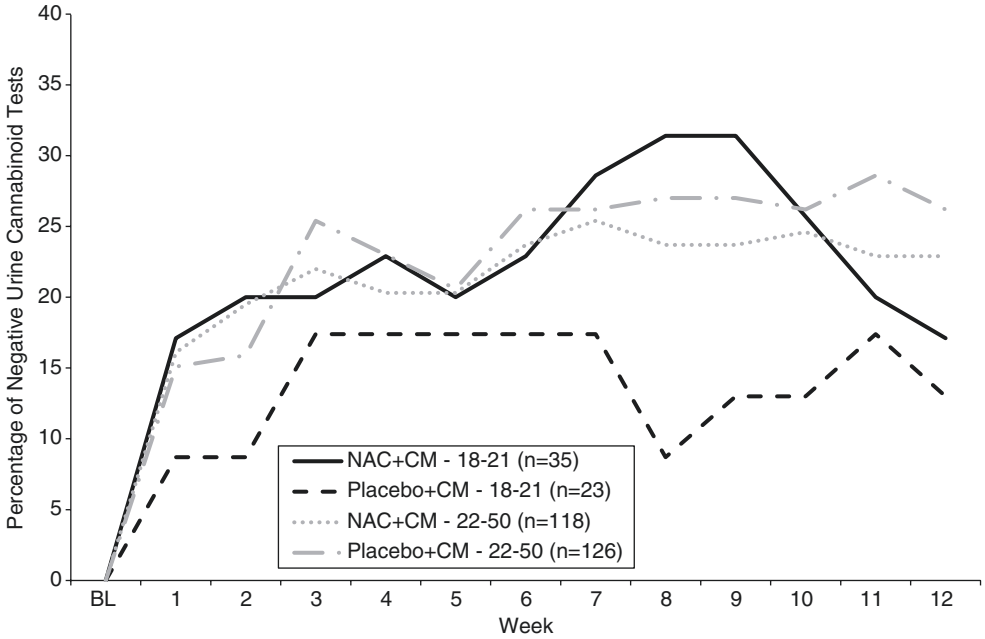

Fig. 22.4 Age and intent-to-treat urine cannabinoid tests in the adult trial

The adult study had an age overlap with the prior adolescent study (ages 18–21). A post hoc comparison within this age group in the adult study was done for comparison with prior adolescent findings. While the small sample size within this age range (n = 35 in the NAC group and n = 23 in the placebo group) yielded insufficient statistical power for formal comparison, NAC participants had a numerically doubled rate of abstinence compared with placebo participants (odds ratio = 2.03, 95% confidence interval = 0.70–5.86, p = 0.187), a magnitude similar to that seen in the adolescent trial (Fig. 22.4).

Paralleling methods examining alcohol outcomes in the prior adolescent trial, we examined co-occurring alcohol use within the adult trial [31]. While changes in cannabis use amounts were not correlated with alcohol use variables, the NAC group, compared to the placebo group, had increased odds of weekly alcohol abstinence (odds ratio = 1.37; 95% confidence interval = 1.06–1.78; p = 0.019), fewer drinks per week (risk ratio = 0.67; 95% confidence interval = 0.48–0.99; p = 0.045), and fewer drinking days per week (risk ratio = 0.69; 95% confidence interval = 0.51–0.92; p = 0.014). Overall, these findings indicated a roughly 30% reduction in

alcohol use among NAC participants, suggesting the need for further trials of NAC focused on alcohol use.

Discrepant cannabis use outcomes between the adolescent study (positive primary efficacy finding) and adult study (null primary efficacy finding) suggest that response to NAC may be age-dependent, with adolescents up to age 21 benefiting and adults not yielding benefit at the 1200 mg twice daily dose. Of note, baseline urine cannabinoid testing revealed a mean of 417 ng/mL in the adolescent trial, compared with 1078 ng/mL in the adult trial ($p < 0.0001$). Combining participants ages 21 and younger between the two trials, the mean baseline urine cannabinoid level was 571 ng/mL, compared to 1141 ng/mL in participants over age 21 ($p < 0.0001$). This suggested that younger participants presented with lower levels of baseline cannabis use than older participants, though baseline frequency in days of use was similar between the two studies – 23/30 days in the adolescent trial versus 26/30 days in the adult trial prior to enrollment.

Whether differences in the findings of the two trials are due to developmental differences in the course and phenomenology of CUD, differential effects of NAC based on stage of brain development, potential need for dose adjustment based on age, differences in medication adherence, and/or other factors remain unclear and are deserving of further examination.

Ongoing Work and Future Directions

We are currently conducting a placebo-controlled trial of NAC for CUD in older adolescents (R01DA042114). This trial is designed to offer an opportunity for replication of the prior adolescent findings but with a different platform treatment. Given that CM was embedded in both prior randomized controlled trials, it is not yet clear whether NAC may be efficacious without embedded CM. The current trial, with enrollment ongoing, includes randomization to receive a 12-week course of NAC 1200 mg twice daily versus placebo, on a platform of weekly medical clinician-delivered brief cessation counseling. While there is evidence of potential synergy between CM and pharmacotherapy [10] and possible need for initial abstinence for NAC to exert relapse prevention effects [6, 8], there is also the potential for NAC to exert effects on acute withdrawal symptoms [7]. Additionally, given that CM is not readily available in many clinical settings, it is important to determine if NAC can exert therapeutic effects without an embedded CM platform. If a positive efficacy finding is yielded, this would bolster translation to real-world clinical settings, in which brief medical clinician-delivered cessation counseling may be reasonably delivered in the context of medication management.

Our group is conducting additional work with NAC among adolescents and adults, targeting tobacco use, alcohol use, cocaine use, and co-occurring psychiatric disorders such as posttraumatic stress disorder and bipolar disorder. We are using cross-translational designs with preclinical and human laboratory/neuroimaging collaborators to optimize our understanding of NAC's neurobiological and behavioral mechanisms and its implementation as a clinical therapeutic agent ([1, 7, 21]; R01AA025086; R01DA038700; R01AA025365; R34DA042228; R01DA034054; K23AA025399; W81XWH13-2-0075). Though findings to date are mixed between adolescent and adult trials of NAC for CUD, our hope is that this line of investigation will provide a template for development of other potentially promising prodrugs for CUD treatment.

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Non-pharmacological Treatments for Cannabis Use Disorders

23

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Introduction

According to data from the National Survey on Drug Use and Health (NSDUH), over four million people in the United States met criteria for CUD [10]. Cannabis use among youth and young adults represents a pressing public health concern. Pointing to epidemiologic data on primary substances of abuse, cannabis ranks third behind alcohol and opioid use among those 12 years and older. Moreover, cannabis remains the most common primary substance reported for treatment admissions among those younger than 20 years. Interestingly but not surprisingly, of the vast majority of individuals with a CUD in the past year, less than 8% received any type of treatment for quitting cannabis and related problems. Taking into consideration the continuum of use, rates of *any* treatment uptake for mild, moderate, and severe CUD are 4.1%, 6.0%, and 15.7%, respectively [23].

Given the changing legal status of cannabis in the United States, the number of individuals who seek treatment for CUD is projected to rise consequently. This coupled with softening perceptions about the potential harms and difficulties associated with problematic cannabis use also will contribute to the expected growth patterns. For example, rates of heavy cannabis use and the development of CUDs have increased over the past 10 years [22]. It is also expected that with the increased rates of use, the number of individuals seeking treatment for CUD will also rise [3]. Elements that may contribute to more individuals seeking treatment for cannabis use problems are the higher potency cannabis products, novel means of use, as well as increased access [7].

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Given the parallels with other substance use disorders, it is not surprising that the treatment research literature focused on interventions for CUD has investigated similar approaches to those studied for other substances. Of the psychosocial interventions, behavioral approaches such as motivational enhancement, cognitive behavioral therapies, and contingency management have received the most study. With adolescents, multiple types of family-based interventions have been developed and tested, in addition to similar evidence-based behavioral approaches used with adults.

Evidence for the Effects of Treatment of CUDs

Psychosocial intervention approaches for CUD are based on treatment strategies that are applied more broadly for treatment of other substance use disorders. CUD psychosocial treatments are usually time-limited, 1–12 sessions, although there are some approaches that continue for significant lengths of time or are considered lifetime treatments (e.g., cannabis anonymous; CA). CUD treatments vary in regards to delivery format, individual vs group. Regardless of modality, the psychosocial treatments for CUD that have the strongest clinical trial research to support their efficacy tend to be based on cognitive behavioral (CBT) techniques, motivational enhancement strategies, and/or contingency management principles. Consistent with treatments designed to target other substance use disorders, psychosocial treatments for CUD show medium effect sizes for reducing cannabis use compared to control conditions [13, 15], although abstinence rates remain low following treatment [44].

Consistent with other substance use treatments, dropout from treatments that consist of multiple sessions for cannabis use is moderate to high (e.g., [11]), and across trials more than 20% of participants are lost to long-term follow-up [19]. It should be noted that in several randomized clinical trials active treatments do not differ significantly from one another in predicting outcomes (e.g., [8, 48]), suggesting

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that there is not currently a gold standard treatment for CUD but instead several viable and effective options [38]. Specific psychosocial interventions for CUD and the randomized clinical trial evidence supporting their efficacy will be reviewed below.

Randomized Clinical Trials

Cognitive Behavioral Therapy/Relapse Prevention

Similar to general CBT approaches, including those for substance use more broadly (e.g., [33]), CBT and relapse prevention for CUD focus on identifying and modifying beliefs and behaviors that are conceptualized as triggering or maintaining of cannabis use behavior. In addition, there is an emphasis on identifying external or environmental triggers that lead to problematic cannabis use in order to modify circumstances that result in substance use. Finally, in CBT and relapse prevention treatments, coping skills and problem-solving techniques are taught in order to help the individual learn alternative, more adaptive responses to thoughts, feelings, and situations that are leading to cannabis use. CBT for cannabis use is short-term and has been tested in as short as 1 session [11] and as long as 14 session protocols [48]. CBT has been tested in both group [40, 48, 49] and individual [8, 11] formats.

In randomized clinical trials, CBT has been shown to be moderately effective for decreasing frequency of cannabis use, promoting abstinence from cannabis use, and reducing cannabis related problems [8, 11, 40, 48, 49]. Follow-up out to 16 months posttreatment demonstrates the lasting benefits of CBT for cannabis use [48]. However, it should be noted that although superiority in comparison to waitlist control is a robust effect in the above trials [11, 48], CBT approaches have not shown superior effects to treatment as usual [40, 49] or other active treatment comparison conditions such as brief motivational interviewing [48] and contingency management [8], suggesting that CBT may not be indicated over other treatment approaches.

Motivational Enhancement Therapies

Treatments that focus on enhancing motivation to change are based on principles of motivational interviewing, a widely used approach for substance use disorders and other related behaviors (e.g., HIV treatment adherence) [35, 36]. Motivational interviewing seeks to build motivation to change a problematic behavior by using a nonjudgmental, open, and empathic therapy environment to increase ambivalence to change, increase self-efficacy, and ultimately make positive changes in regard to the problem behavior. Skills such as asking open-ended questions, reflection of thoughts and feelings, summarizing, and highlighting ambivalence are used (e.g., [35, 37]). Personalized feedback components and education regarding substance use behavior is commonly added to motivational interviewing techniques, and resulting therapy approaches are termed motivational enhancement therapies (MET; [35]).

These components provide patients with structured feedback regarding their own substance use patterns, often compared to norms of a meaningful reference group (e.g., peers), and other information regarding their individual risk profile. Motivational enhancement therapies have the benefit of being a short-term treatment approach, often being delivered in one to two treatment sessions, and can be delivered in settings as diverse as outpatient clinics, inpatient treatment settings, and hospital emergency rooms or other hospital-based settings. Furthermore, motivational enhancement therapies can be used with non-treatment-seeking individuals given the explicit emphasis on increasing motivation to change.

Motivational enhancement protocols for cannabis use have demonstrated modest efficacy in reducing cannabis use in treatment-seeking adults, with a two-session MET protocol demonstrating similar effects to a 14-session CBT protocol [48]. In addition, several randomized controlled trials demonstrate the efficacy of MET for reducing cannabis use and related problems in non-treatment-seeking adolescents/young adults [2, 51, 52] and adults [46, 47] at follow-up periods ranging from 3 to 12 months. In these randomized studies, MET was more effective than delayed treatment controls [46, 47], assessment only [2], and an educational feedback control group [47]. However, in two studies with non-treatment-seeking adolescents, MET did not outperform an educational feedback condition at either 3-month [51] or 12-month follow-up [52].

Contingency Management

Contingency management interventions are reinforcement based and seek to promote decreases in substance use by providing explicit positive reinforcement, in the form of tangible rewards (e.g., monetary compensation, inpatient treatment privileges) for abstinence or treatment compliance. A distinct disadvantage of contingency management approaches is that they are often not feasible in many clinical settings due to costs associated with providing rewards. Still, one study [4] that looked at a stand-alone contingency management treatment that provided monetary vouchers for abstinence, confirmed via urine toxicology tests, showed relatively strong effects in promoting abstinence during treatment (55% marijuana-negative urine specimens) compared to cognitive behavioral therapy with (43% marijuana-negative urine spec-

imens) and without (32% marijuana-negative urine specimens) contingency management. Similarly, Kadden et al. [29] demonstrated that contingency management alone showed the highest rates of abstinence at posttreatment compared to both other active treatments (CBT and MET; CBT, MET, and contingency management) and a case management control group. However, these superior effects of contingency management were not maintained at 12-month follow-up in either study, and it appears that adding CBT to contingency management may be necessary to maintain gains [4, 29].

Combined Treatments: Cognitive Behavioral, Motivational Enhancement, and Contingency Management Therapies

The most robust literature for treatment of cannabis use is for clinical trials that investigate cumulative benefits of multiple approaches combined (e.g., [44]). Delivering treatment protocols that combine multiple evidence-based techniques requires substantially more expertise and training resources on the part of the therapist and is also higher burden for patients. However, approaches with multiple components also appear to improve outcome. In one of the largest randomized controlled trials conducted to date (n = 450), cannabis-dependent adults receiving a combination of MET, CBT, and case management (9 sessions) reduced cannabis use and associated problems more than those receiving either MET alone (2 sessions) or waitlist control at posttreatment and at 15-month follow-up [1]. In other trials, protocols that combine CBT, MET, and/or contingency management techniques demonstrate reduced use and higher rates of abstinence from cannabis when compared to delayed treatment control conditions [26–28, 34] or to protocols using fewer strategies [4, 5, 9, 29, 45]. One exception in demonstrating the superiority of combined treatments is a randomized clinical trial [8] of young adults, most of whom were referred by the criminal justice system for treatment, which found that CBT alone led to greater reductions in cannabis use compared to CBT combined with vouchers for treatment adherence and compared to an abstinence-based voucher program enhanced with CBT. Similarly, a study of CBT and MET combined with either contingency management for abstinence or homework completion did not differ from a case management control group, with all three treatment conditions leading to moderate decreases in cannabis use and problems [32].

Mindfulness Meditation

Mindfulness and meditation treatments are applied broadly for substance use (e.g., [53]) and consist of teaching strategies to control attention to focus on the present moment and are targeted at increasing awareness and nonjudgmental acceptance of current emotional states in order to increase tolerance of negative affect that might trigger substance use. Only one small randomized controlled trial has looked at the treatment of cannabis use by using mindfulness meditation in combination with motivational interviewing. DeDios and colleagues [14] found significant reductions in cannabis use (number of days used) for young adult females who completed motivational interviewing and mindfulness meditation compared to an assessment only control group at 3-month follow-up. Additional studies exploring this approach are needed to confirm efficacy for cannabis use specifically.

Family Support and Multidimensional Family Therapy

Additional approaches for adolescent cannabis use have focused on intervening with the family in order to address risk factors for substance use that occur in multiple systems for the patient (e.g., family, school, peers). Of these types of approaches, multidimensional family therapy (MDFT; [31]) which focuses on engaging the family, establishing goals, focusing on key adolescent and family themes (e.g., communication, trust/mistrust), and preparing skills for the future while incorporating substance use into the treatment approach is the most widely studied for cannabis use. MDFT as applied to cannabis use involves integrating substance use treatment practices into family therapy. In the large Cannabis Youth Treatment Project, two randomized controlled trials demonstrated that MDFT and family support therapy, a form of family therapy that integrates family therapy into a MET and CBT approach to decreasing cannabis use in adolescents, were as effective at promoting abstinence and recovery from cannabis use at 1-year follow-up as both short (5-session) and long (12-session) forms of CBT combined with MET. Adolescents receiving MDFT showed similar reductions in cannabis use as those receiving CBT at 1-year follow-up, although there was some evidence that for those with higher baseline severity of use, MDFT was more effective [24]. Similarly, adolescents receiving MDFT showed less cannabis dependence compared to adolescents in a comparison individual psychotherapy condition at 1-year follow-up [39].

Twelve-Step Facilitation (Marijuana Anonymous)

Twelve-step facilitation groups, such as alcoholics anonymous (AA) and its related groups, including marijuana anonymous (MA), is one of the most widely disseminated

treatment approaches for substance use, at least partly due to its format as a free, self-help, community-driven program. Based on disease models of substance use and the explicit goal of abstinence, AA has been shown to be as effective as motivational enhancement therapy for alcohol use [21]. However, no clinical trials have looked specifically at efficacy of MA programs and efficacy of 12-step programs for cannabis use remains unknown.

Web-Based or Telephone-Based Delivery

Computerized and telephone-based interventions are cost-effective, flexible modes of treatment delivery that have been shown to be effective in treatment of substance use disorders [41]. In a randomized controlled trial conducted in Australia [20], cannabis users over the age of 16 were randomly assigned to a four-session telephone-based CBT and MET intervention or to a delayed treatment control group. Those in the telephone intervention group showed significantly less cannabis dependence, use, and problems at 12-week follow-up, demonstrating initial promise of a phone-based approach.

To date, two randomized clinical trials have examined computerized approaches for treating cannabis dependence. Rooke et al. [42] found that a computerized version of CBT and MET was superior to a waitlist control at 3-month follow-up. In a separate study [30], a personalized feedback intervention was not superior to an assessment-only control group on cannabis use outcomes at posttreatment or 6-month follow-up. In the one existing study that compared computerized and in-person modalities, Budney and colleagues [6] used a non-randomized design to test computer-based delivery of a combined treatment (contingency management, MET, and CBT), compared to standard therapist-delivered combined treatment for cannabis use. Participants were not randomly assigned and sample sizes in the study were small. Despite the preliminary nature of the study, importantly there were no significant differences in cannabis outcomes or adherence for the computer-delivered vs therapist-delivered treatments. Additional studies should seek to replicate these preliminary findings to better understand the potential of computer-based programs for the treatment of cannabis use disorders.

Variables Affecting Treatment Outcome

Treatment Specific Factors

In a recent meta-analysis, Davis et al. [13] explored several treatment-specific factors as potentially related to outcomes. They found that treatment modality (group vs individual), number of sessions, and format (in-person vs phone/computer delivery) did not significantly predict differences in effect sizes between studies. This is consistent with published trials that have directly compared shorter- and longer-duration similar treatments (e.g., [1, 11]) and online and in-person interventions [6], showing no significant differences based on length or modality. Of note, spacing of sessions may affect outcome. One study demonstrated that although four sessions of combined CBT and MET spaced out over 3 months showed similar effects on cannabis use compared to the same four sessions spaced out over 1 month, the longer 3-month treatment showed superior effects on reducing dependence and other comorbid substance use [28]. These findings suggest that spacing sessions further apart may lead to more robust treatment effects, although replication is needed.

Baseline Patient Characteristics

There is some evidence that certain individual characteristics may serve as either prognostic or prescriptive predictors of outcome. For example, family history of substance use problems [30] and being in a later stage of wanting to change cannabis use behavior (e.g., [30, 46]) predicted greater response to treatment. Baseline use may predict outcome as submitting a positive marijuana urine test was a predictor of worse outcome and decreased likelihood of achieving abstinence with treatment [9]. In an examination of differential predictors of CBT vs MDFT in adolescents, older age and a lack of co-occurring psychopathology predicted better outcomes in CBT, while younger age and presence of a comorbid disorder predicted better outcomes in MDFT [25]. Additional studies that seek to understand which treatment approaches work best for whom are needed to better inform clinical decisions.

CUD Treatment Optimization Through Mechanisms of Behavior Change

Research on mechanisms of behavior change that are activated by efficacious and effective treatments have important implications. Behavior change mechanisms are essential to achieve short- and long-term treatment success and establish key optimization parameters. Other implications of this work are the potential of identified mechanisms to contribute to the development of more potent treatments, as well as establish possible determinations regarding dose and timing. In addition to their application to the etiology of cannabis use behavior, decision-making processes (e.g., impulsivity, temporal discounting, reinforcement pathology, inhibitory control) are being actively studied in the context of improving cannabis treatment outcomes [12]. For example, as candidate

mechanisms of behavior change, decision-making processes have been guided by the experimental medicine approach. This approach seeks to answer the question, "what are the mechanisms or processes that drive behavior change?"

There are three essential elements to this approach. First, the overarching research question must be driven by hypotheses about specific malleable targets (e.g., decision-making or the broader spectrum of self-regulation) that, if altered, can lead to changes in outcomes. An additional requirement is methods or treatments that engage the proposed target mechanism. Third, valid measures of those processes, for example, measures to evaluate the extent to which the target mechanism has indeed been "engaged" and, ultimately, its engagement is related to change in cannabis use outcomes. All three elements are critical steps for understanding mechanisms that can maximize efficacy and optimization.

With regard to research efforts to improve and expand the treatment pipeline for CUDs, increased potency of treatments can be achieved if optimization strategies engage a behavioral target hypothesized to be responsible for change. To highlight support of such activities, the National Institutes of Health (NIH) Science of Behavior Change (SOBC) Common Fund initiative spearheads a research network to test hypotheses about how behavior change is achieved and understand the mechanisms responsible for change.

This can be contrasted with traditional efficacy testing. In addition, to test whether a treatment "works" as hypothesized, valid measures of target engagement are essential. The experimental medicine approach also has implications for measures development. Measures at multiple levels—behavioral, biological—are being tested or developed in the SOBC program to provide a convergence of evidence, increasing support for hypotheses and confidence that measures are valid. Approaches to manipulate or engage these targets, to demonstrate that they are malleable, and to optimize target engagement are also required.

Behavior Change Target Classes

Germane to non-pharmacological treatments for cannabis use, the SOBC Network has classified three broad classes of candidate targets that are conceptually distinct from each other but highly relevant to understand the mechanisms by which behavior is changed. Three target classes of *self-regulation*, *stress resilience and stress reactivity*, and *interpersonal and social processes* were identified as being both central to behavior change and ready to contribute to an evidence-based approach to the design of behavioral treatments. Identification of these three areas relied foremost on the strength of existing research demonstrating their promise, their relevance across multiple clinical endpoints, and their fit within the experimental medicine approach. A summary of each of the target classes will be discussed in turn below.

Self-Regulation

Although not much has been done specifically on self-regulation and cannabis, this target mechanism should be explored as it encompasses a wide range of behavioral and psychological constructs and processes [16, 50]. These processes include, but are not limited to, conscientiousness, self-control, response inhibition, impulsivity/impulse control, behavioral disinhibition, temporal discounting, emotion regulation, cognitive control (including goal selection, updating, representation, and maintenance; response selection, inhibition, or suppression; and performance or conflict monitoring), cognitive/emotional homeostasis, effort modulation, and flexible adaptation.

Measures of these processes have been developed at many levels of analysis and across a diverse set of scientific fields, using techniques such as self-report instruments, field-based approaches (e.g., ecological momentary assessment), and direct assessments of cognitive (e.g., stop-signal task) and behavioral (e.g., temporal discounting tasks) components of self-regulation, as well as indirect measures such as the effect of reappraisal strategies on emotional function. A variety of other-report and observational approaches exist. For example, informant reports of emotional regulatory skills, temperament, and behavior. Also common are a range of neuroimaging and electrophysiological assessments, ranging from assessment of properties of prefrontal-parietal and prefrontal-subcortical control networks to measures of heart rate variability.

Despite a lack of a consistent ontology for self-regulation, many treatment approaches that purport to engage or change self-regulatory processes have been developed and tested. The extent to which these targets are isolated as crucial mechanism of change in substance use treatment, including treatment for CUD, has not adequately been teased apart [43]. The complexity of self-regulation at the psychological and behavioral level also is reflected at the neurobiological level.

A range of region-level brain targets have been implicated in self-regulation, which may function as components of one or more interconnected circuits or networks. Device-based interventions (e.g., transcranial magnetic stimulation) that target these networks may hold great utility, but have not yet been tested in substance using samples. Researchers continue develop a functional ontology of self-regulation mechanisms and identify common mechanisms across multiple laboratory paradigms for target-oriented treatments to improve cannabis use outcomes.

Stress Resilience and Stress Reactivity

Stress is defined as a real or perceived imbalance between environmental demands and an individual's capacity to adapt to these requirements. Stressors, or stress exposures, are potential or actual threats or challenges to an individual. Studies have demonstrated stress coupled with long-term cannabis dependence is associated with resistance to change and relatively poorer treatment outcomes. The taxonomy for stressors includes, for example, major traumatic events; acute, novel, or unpredictable situations; repeated or chronic challenges; and daily "hassles." Individual responses to stressors vary in nature, quality, and temporal characteristics. The initial and acute response to a stressor includes *stress reactivity* and *recovery* of those systems, with different time courses for distinct components (e.g., neural, physiological, cognitive affective, and behavioral) of the response.

Stress resilience refers to the dynamic multidimensional process encompassing positive adaptation within the context of the stressor or adversity. Stress reactivity and stress resilience are believed to be causal mechanisms or crucial intermediate phenotypes in the development of cannabis use disorders [17]. Individual differences in patterns of stress reactivity and stress resilience affect cannabis use onset, level of dependence, and treatment prognosis. Therefore, treatment efforts should take into account the variability of stress responses and/or outcomes through manipulation of stress response.

Interpersonal and Social Processes

Processes in interpersonal and social contexts shape behavior formation, maintain current behaviors, and have the potential to reinforce or deter cannabis use change efforts. Treatments that target these processes can motivate and maintain substance use behavior change. Indeed, interpersonal and social processes encompass a broad class of potential targets of behavior change. This broad class of targets can be unpacked into multiple targets that have varying degrees of conceptual overlap with each other and can be grouped in different ways. For example, the following promising targets for behavior change could be considered related or overlapping concepts within the broad categories of culture (acculturation, collectivist vs individualist, cultural orientation, workplace culture), social-emotional processes (affection, dyadic coping, emotional/social contagion, emotional social support, empathy, expressed emotion, hostility, social emotion regulation, social threat attenuation), social identity (self-affirmation, sense of belonging, social self-identity), social relationships (attachment, caregiving, family hierarchies, exclusion, instrumental social support, rejection, social isolation, stigmatization/shame, discrimination), social shaping (linking individual outcomes to group-level consequences, recasting, role modeling, parental monitoring or supervision, positive reinforcement, setting expectations, social/group norms, social reinforcement), and power (coercion/force, criticism, institutional social control, overprotectiveness; [18]).

Interpersonal and social processes have been measured in a variety of ways, but work is needed to develop and test measures that can be used to verify engagement of specific interpersonal or social targets. Given the wide range of interpersonal and social processes implicated in health behavior change, as well as the overlap among targets, it has proven difficult to measure these targets consistently in the laboratory, in clinical trials, or in large-scale observational studies. Such measures will allow researchers to develop new or refine existing treatments designed to engage interpersonal and social targets. Also, more refined measures would allow for researchers to more precisely assess whether these interventions effectively engage interpersonal/social processes and the extent to which engagement translates into short- and long-term cannabis abstinence. This work can ultimately lead to future, large-scale interventions designed to engage interpersonal and social targets related to behavior change and facilitate more sustained initiation and maintenance of cannabis abstinence.

Conclusions and Future Directions

Across the available treatment options for CUD (e.g., motivational enhancement therapy, cognitive behavioral therapy, contingency management, multidimensional family therapy, combined therapies), psychosocial treatments compared to no treatment consistently produced significant reductions in quantity, frequency, and severity of cannabis use as well as severity of dependence symptoms [13, 19]. Generally, the extant literature suggests that more intense treatments over longer intervals (i.e., four or more sessions) appear more robust than the briefer motivational approaches, but future studies are necessary to better determine adequate or optimal durations of treatment. Also important is the observation that the great majority of those receiving treatment do not achieve cannabis abstinence for substantial durations of time and many of those who do relapse within a month posttreatment.

By virtue of changing legal status of cannabis in the United States, the number of individuals who seek treatment for cannabis use disorder is projected to rise as a consequence. Therefore, non-pharmacological treatment options must be available to meet this need. Based on the current review of the cannabis treatment literature, the approaches used for other substance use disorders appear to produce similar outcomes for CUD. Continued efforts to produce efficacious and effective approaches are needed, specifically,

treatment development and evaluation that integrate novel targets of behavior change. As outlined in this chapter, self-regulation, stress reactivity/stress resilience, and interpersonal/social processes are candidate mechanisms of behavior change that might involve the development of more efficient and potent interventions. Additionally, treatment studies that target mechanisms germane to cannabis use may provide information on treatment specificity to better match patients with treatments that offer strategies that best meet their needs or offer specific treatment strategies that better engage nonresponders.

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Mindfulness-Based Practices for the Treatment of Cannabis Use Disorder

24

David Shurtleff

Introduction

The popularity of complementary and integrative health approaches such as meditation and mindfulness-based practices has grown in recent years, as many turn to these self-care practices to help relieve stress and anxiety. Meditation and other mind and body approaches have been used for centuries to increase calmness and physical relaxation, improve psychological balance, cope with illness, and enhance overall health and well-being. In the last decade or more, an area of research on mindfulness-based practices has focused on the neurobiological mechanisms underlying these approaches and their impact on mental and physical health. Mindfulness meditation has been used as part of a treatment plan for a range of health conditions, including pain, high blood pressure, irritable bowel syndrome, anxiety, and depression. Mindfulness-based approaches have also shown some success when applied to the treatment of substance abuse and addiction. Although currently there is little research that directly examines the efficacy of contemplative meditative practices for cannabis use disorder (CUD), many symptoms associated with cannabis withdrawal such as irritability, anxiety, and depressed mood may be improved through meditative practices.

Definitions and Scope

Complementary health approaches include a broad range of practices, interventions, and natural products, which are not typically part of conventional medical care or which may have origins outside of usual Western practice. *Complementary* approaches are defined as those used together with conventional therapies, distinguishing them from *alternative* practices, those used as a substitute for standard care. Complementary practices can roughly be divided into two major groups—natural products and mind and body practices. Natural products include a diverse group of orally or topically administered substances such as botanical products, unconventional diets, dietary supplements, herbal medicines, probiotics, and others. Mind and body practices and disciplines are usually administered by or taught to others by a clinician, trained practitioner, or teacher and include acupuncture, massage, meditation, and hypnosis. Acupuncture, massage therapy, meditation, relaxation techniques, spinal manipulation, and yoga are examples of mind and body practices [40]. These approaches are being used more frequently in mainstream health-care facilities for both patients and health professionals.

The term *integrative health* care emphasizes a patient-focused approach to health care and wellness. Most integrative health care is team-based, often bringing conventional and complementary approaches together with self-care in a coordinated way [40]. Physicians advocating this approach generally included selected complementary health practices in the care they offer patients, and many have established practice settings that include complementary health practitioners.

Patterns of Use

The National Health Interview Survey (NHIS), a large, national household survey of health practices conducted by the National Center for Health Statistics, a component of the Centers for Disease Control and Prevention, has addressed the use of complementary health practices in 2002, 2007, and 2012. The NHIS survey uses methods that create a nationally representative sample and has a sample size large enough to permit valid estimates about some subgroups. In the 2012 survey, 32.2% of adults and 11.6% of children had used one or more modalities [6, 16]. The most prevalent mind and body practices, according to the survey, are yoga,

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chiropractic or osteopathic manipulation, meditation, and therapeutic massage [6, 16]. Americans are willing to pay for these services; the estimated out-of-pocket expenditure for complementary health practices in 2012 was $30.2 billion ($28.3 billion for adults and $1.9 billion for children), representing 1.1% of total health expenditures and 9.2% of out-of-pocket costs [38].

There are a variety of reasons why people choose complementary health approaches. An analysis of data from the 2012 survey showed that people who practice yoga (a mind and body approach) or who take natural product supplements are more likely to do so for wellness-related reasons rather than for treating a specific disease or condition. Although perceived reasons and self-reported perceived health outcomes vary by type of complementary health approach, in general, individuals reported that complementary health approaches improved their overall health and made them feel better [51].

The popularity of meditation has grown in recent years, and there is an apparent increasing interest in using this self-care practice to reduce stress and anxiety. In the 2007 NHIS survey, nearly 13% of adults reported doing deep breathing exercises, which has been interpreted as meditative practice. The popular media has promoted and shown interest in information about how these mind and body approaches may be used and integrated into everyday life [41].

Origin of Meditation and Mindfulness-Based Practices

Meditation, a mindfulness-based practice, is described as a "mind and body" approach that has a long history of use for increasing calmness and physical relaxation, improving psychological balance, coping with illness, and enhancing overall health and well-being. Mindfulness focuses on the interactions among the brain, mind, body, and behavior [40].

Meditative practices emanating from Buddhist religious tradition were originally used to seek a path to "awakening" [30]. This tradition suggests that mindfulness, emerging from meditative practice, leads to reduced suffering and increased well-being [26]. Mindfulness meditation derives from the teachings of the Buddha and the Chinese notion of Tao [27]. In Sanskrit, it was called "dharma," which translates to lawfulness as in "the laws of physics." Mindfulness meditation was used to explore the nature of the human condition and to treat three fundamental "disease" states: greed, hatred (aversion), and ignorance/delusion (unawareness) [27].

In recent years, meditative practices have been examined within the framework of the modern Western disciplines of psychology and neuroscience [31, 33, 37], investigating their underlying cognitive processes and neurophysiological mechanisms. It has recently been proposed that a new discipline of contemplative science should be developed and expanded to the study of meditative practices that come not only from but outside Buddhist tradition, to more fully contribute to psychological, cognitive, and neuroscience research [19]. In this research context, meditative practice has been conceptualized as an array of complex emotional and attentional regulatory training regimes designed to promote well-being and emotional balance [31]. Mindfulness-based approaches attempt to foster a nonjudgmental awareness, curiosity, openness, and acceptance of internal and external experiences, with the intended goal of eliciting greater reflection and acceptance, especially regarding negative affect [42].

Among these various mindfulness-based practices, two types are commonly studied—focused attention meditation and open monitoring meditation (OM). Focused attention meditation involves focusing attention on a chosen object to reduce wandering, and OM meditation involves nonreactive monitoring of moment-to-moment experience, being aware moment to moment of thoughts or feelings that occur in personal experience without focusing on an explicit object. OM is often the next step after the ability to focus attention is stabilized. This monitoring is nonreactive and nonjudgmental [31, 37]. Attentional components of mindfulness have also been described as the ability to attend to one object for extended periods of time, to shift between mental states consciously, and to inhibit thoughts and sensations [45]. A third type of meditation called loving-kindness meditation attempts to enhance sympathetic joy and to increase altruistic behaviors [31].

Practically, mindfulness-based approaches such as mindfulness-based stress reduction (MBSR) developed by Jon Kabat-Zinn in 1979 at the University of Massachusetts, and other related contemporary mindfulness-based interventions, focus on training to be attentive in day-to-day life, "living in the movement" while, at the same time, encouraging an attitude of acceptance of events and experiences [45]. MBSR, for example, is an 8-to-10-week structured intervention, group program. A session occurs once a week with a single all-day session per course on a weekend day. Each session is devoted to a topic or exercise that includes mindfulness meditation practices, mindful yoga postures, and mindfulness coping strategies during stressful situations and social interactions. To improve the likelihood of participant proficiency, participants are expected to engage in daily 45-min homework assignments primarily in the form of meditation practice, mindful yoga, and applying mindfulness to situations in everyday life [25].

Meditation is the practice used to develop mindfulness, which has been hypothesized to consist of three core interwoven elements or axioms: attention, intention, and attitude [45]. The elements of attention have been described previously. The role of intention describes an individual's

goal or purpose for engaging in the practice, which may change over time. A common first intention may be to improve self-regulation, which over time may change to self-exploration. The attitudinal element involves an openness and acceptance of experiences, without evaluation or interpretation.

Cognitive and Neurobiological Underpinnings

Functional magnetic resonance imaging (fMRI) studies are beginning to provide a detailed understanding of the brain activity patterns associated with meditation [20, 31, 37]. For example, a 2007 study by Brefczynski-Lewis and colleagues found distinctive neural activation of multiple brain regions with focused attention meditation. The strongest activation was in attention-associated brain regions such as the dorsolateral prefrontal, visual cortex, and the superior frontal sulcus and intraparietal sulcus [10]. Other neuroimaging meta-analyses have shown regions of deactivation in areas including the ventral posterior cingulate cortex associated with episodic memory and left inferior parietal lobule associated with conceptual processing [20, 37]. What can be surmised from an extensive review of the extant data is that mindfulness practices, in general, can increase functional connectivity between the posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (vmPFC) default network regions, which may represent greater monitoring and evaluation of thought, a key aspect of meditative practice. Another common finding is increased functional connectivity between the dorsolateral PFC (DLPFC) and the insula. The DLPFC has been linked to the executive network associated with several cognitive activities, including aspects of working memory, judgment and decision making, responding to changing task demands, inhibition, planning, and focused attention. The insula is associated with the salience network and is involved in enhanced body awareness and in the ability to shift attention, other key elements of meditative practice.

An additional meta-analysis from OM studies indicates not only an activation of the insula involved with somatic signals but also activation of the left inferior frontal gyrus (pre-supplementary motor area), supplementary motor area, and premotor cortex associated with motor control and movement [20].

Further, mindfulness-based interventions have been shown to decrease amygdala activity in socially anxious patients [22]. Similarly, amygdala activity was reduced in response to negative emotional images in healthy adults following mindfulness training [18].

The recruitment of executive and somatosensory awareness and modulation of emotional regions suggests that, at their core, mindfulness-based practices can change these key brain regions in significant ways. The practice is effortful and requires sustained attention on sensory and emotional experience. Engaging and strengthening these emotional and cognitive control systems may be useful for treating many aspects of CUD.

Application to CUD/SUD

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* CUD involves significant impairment in multiple areas of functionality as well as the development of tolerance and withdrawal to marijuana [2]. Symptoms associated with cannabis withdrawal include irritability, anger, or depression; nervousness or anxiety; and restlessness or depressed mood. Although little research has directly examined the efficacy of contemplative, meditative practices for CUD, mindfulness-based approaches have been applied to the treatment of substance abuse and addiction [7, 12, 13, 17, 29, 34, 35, 52].

Mindfulness-based approaches for substance abuse treatment, in part, attempt to decrease the impact of negative affect, which is thought to serve as a trigger for substance use [50]. Improving distress tolerance is an important aspect of mindfulness-based substance abuse treatment. Mindfulness training can also focus on drug craving and reactive behavior, bringing an awareness of craving and automatic response and actions, and therefore providing an alternative contemplative approach to cope with urges to use a drug. In behavioral terms, mindfulness-based approaches for substance abuse can be thought of as a process of desensitization to negative affect. Over time, with mindfulness strategies, exposure to drug associated cues can facilitate extinction of automatic negative emotions and subsequent substance use [8].

Results from studies of other mental health conditions lend additional support for the potential efficacy of mindfulness-based practices for treating CUD and SUD. Mindfulness-based approaches have been shown to be potentially useful in reducing stress for the treatment of anxiety and depression [24, 42] and emotion dysregulation [32]—known risk factors for SUDs—and may also be useful in addressing co-occurring substance use and mental health disorders [54].

Working with the general principles of meditative practices, treatments involving the fostering of mindfulness have been used to address the practical needs of patients with SUD. There is only one published report, however, testing the feasibility of contemplative, meditative practices for marijuana abuse [17]. In this pilot study, de Dios and colleagues examined whether motivational interviewing combined with mindfulness meditation would reduce marijuana use among women, 18–29 years of age. Volunteers were

assigned to a motivational intervention and mindfulness-based mediation (MI-MM) condition (n = 22) or an assessment-only condition (n = 12). The MM intervention comprised components from MBSR and mindfulness-based cognitive therapy for depression. MM training involved both an audio CD to take home for daily practice and two intervention sessions led by a certified MBSR instructor. The sessions were 2 weeks apart. Subject-specific estimates of days using marijuana 1, 2, and 3 months posttreatment were the primary outcome measure. Seventy-five percent of the study participants assigned to MM reported meditating posttreatment, on average, 8.47 days per month. MM participants reported smoking marijuana, on average 7 fewer days at 1, 2, and 3 months posttreatment than the control group. The authors speculate that MM may have helped the participants better cope with stress and anxiety, which may have resulted in reduced marijuana use. Further, on the days the women in the intervention group practiced meditation, they were half as likely to smoke marijuana. This observation suggests that participants may have used meditation to cope with stress and negative affect, instead of using marijuana [17].

Stress, anxiety, and negative affect are known triggers for marijuana use, as well as use of other addictive substances [36, 49]. To test the role of mindfulness training in reducing stress reactivity in tobacco smokers, researchers examined participants who completed a mindfulness training program or cognitive-behavioral treatment (CBT) for smoking cessation [11, 28]. Overall, the results from the trial indicated that those participants receiving mindfulness training smoked less than those receiving CBT.

In the follow-on study, during an fMRI scanning session, participants listened to either individualized stressful/negative scripts or individualized neutral/relaxing scripts. For all participants, the stressful/negative scripts resulted in stress reactivity characterized by activation of several stress-related brain regions including the amygdala and anterior/mid-insula. Overall, the mindfulness training group showed lower activation in these brain regions than the CBT group. Importantly, individuals with the greatest activity in those regions showed the lowest reduction in smoking from pre-treatment to 3-month follow-up. These data suggest that mindfulness training can lead to a reduction in stress reactivity, a major trigger for drug use and drug abuse relapse.

In a similar study, Bowen and colleagues conducted a randomized three-arm clinical trial to test the efficacy of a mindfulness-based relapse prevention (MBRP) compared to relapse prevention therapy (RP) or treatment as usual (TAU). Participants were recruited from a drug treatment facility that provided 28-day inpatient treatment, 90-day intensive outpatient treatment, and 1-year aftercare treatment. All treatment conditions were held in a group setting [9].

For the MBRP intervention, participants attended eight weekly, 2-h group sessions. Each session included guided meditation and addressed key aspects of mindfulness in the context of substance abuse. The RP intervention was identical to the MBRP intervention in terms of the frequency and duration of the session, format, size, location, and assigned homework. The RP intervention focused on strategies for assessing high-risk situations, coping skills, problem-solving, goal setting, self-efficacy, and social support. TAU was an abstinence based, alcoholics/Narcotics Anonymous 12-step program, which facilitated recovery-oriented discussions in an open group. The TAU groups met one to two times weekly for 90 min [9].

While marijuana use was not directly reported, days of polydrug use 90 days before and 3, 6, and 12 months postintervention were assessed. Heavy drinking days were also captured over the same time points. At the 3-month follow-up, there were no reported significant differences on drug use days, any drug use, heavy drinking days, or any heavy drinking between treatment groups. At 6 months, however, the MBRP and RP participants had a significantly higher probability of abstinence from drug use and less heavy drinking than the TAU participants. At 12 months, there was a significant divergence among RP and MBRP participants. Participants in the MBRP group, compared with the RP group, reported 31% fewer drug days and a significantly higher probability of not engaging in any heavy drinking [9].

An interesting finding of this study is that the beneficial effects of MBRP emerged over 12 months, which may be explained by the participants' improved ability in mindfulness-based practices, leading to a reduction in, or improved coping with, the discomfort associated with craving or negative affect [9]. There is a clear practice effect associated with mindfulness-based approaches, leading to changes in response to internal and external events with associated brain changes [31]. Continued practice can strengthen self-monitoring and improve an individual's overall well-being, resulting in altered brain states, which can lead to improved long-term outcomes, including a decrease in substance abuse.

Research has also suggested that even brief mindfulness-based interventions may be effective in reducing craving and negative affect. Bowen and Marlatt showed that current smokers assigned to receive a 1.5-h mindfulness intervention compared to an unguided coping control group smoked fewer cigarettes over the 7 days following the experimental session. This brief practice effect, while resulting in some short-term benefit, remains unclear whether relatively abbreviated interventions can support long-term behavioral change [8].

In summary, there is a growing body of evidence suggesting that mindfulness-based interventions may be useful and effective for treating SUD and, potentially, although not specifically addressed, CUD. Additional studies focusing on modifying existing mindfulness-based interventions are likely needed to standardize their use for CUD. Although much can be adapted from what is currently known, there is

a need to consider adaptations for treating adolescents with CUD. It is estimated that 2.7% of adolescents have a CUD diagnosis, and there is growing concern about the impact of marijuana use on the developing brain [48]. Mindfulness-based interventions may not only help reduce marijuana use but may have the added value of ameliorating potential cognitive deficits associated with marijuana use.

Using Mindfulness-Based Intervention with Children and Adolescents

Adapting mindfulness-based approaches for children and adolescents with psychiatric disorders has been a focus of recent research. Currently, although many studies are showing acceptability and feasibility of adapting the approaches for children and adolescents, these studies tend to be underpowered and not adequately designed to determine the efficacy of the intervention [14].

Biegal and colleagues, however, conducted a study exploring the usefulness of MBSR training in adolescents with stress-related psychological symptoms (e.g., depression, anxiety, and sleep difficulties) in which participants were randomly assigned to treatment as usual (TAU) group or MBSR in addition to TAU group. MBSR consisted of training in eight weekly classes, 2 h each, and were categorized into three specific domains: intention, attention, and attitude. The investigators also modified the standard MBSR course in a manner suitable to adolescent participants, including a reduction in home practice from 45 min to 20–35 min, elimination of the day-long retreat, and focused presentations and discussion topics on issues relevant to adolescents and those with psychiatric disorders [4].

Results showed that participants receiving MBSR combined with TAU significantly reduced self-reported anxiety, depressive, and somatization symptoms and improved self-esteem and sleep quality compared with TAU-only control participants. In the study-completing MBSR group, there were also significant declines in self-reported perceived stress, obsessive symptoms, and interpersonal problems relative to TAU controls. There was also a significant increase in Global Assessment of Functioning (GAF) scores compared to those receiving TAU alone. Over 45% of the MBSR group participants, particularly those with mood disorder, showed improved diagnostic changes, compared to the TAU control participants. These data suggest that MBSR designed for adolescents can have a positive effect on both self-reported outcomes and clinical measures. This study further suggests that a modified version of MBSR is well tolerated by adolescents with a range of mental health conditions [4]. Over 75% percent of participants assigned to the MBSR arm completed the intervention, which is comparable with completion rates seen with adults [3].

Minority Populations

Given the health disparities associated with access to treatment and treatment outcomes, research addressing mindfulness interventions must address this issue. Studies powered to test efficacy across race and ethnicity are needed. If shown to be effective with diverse groups, mindfulness-based approaches may prove to be an effective approach for improving treatment retention, relapse, and related outcomes [1].

Mindfulness and Drug Abuse Prevention

Mindfulness-based interventions may be useful as part of a drug abuse prevention strategy for children and adolescents. Using these interventions, the goal would be to modulate risk and protective factors that may reduce the likelihood of later problems, such as substance abuse. In this context, mindfulness-based practice may be useful in targeting and strengthening emotional and attentional mechanisms, thereby increasing inhibitory control and reducing the risk for substance use, including marijuana abuse. Research suggests that for adolescents, increases in positive and negative affect have been associated with increased desire to use marijuana [46]. Having the ability to sustain attention and practice nonjudgmental awareness of emotions and the present moment experience may provide an effective coping and regulatory mechanism to reduce or prevent substance abuse.

From a neurobiological perspective, substance abuse risk factors, in part, have been linked to late prefrontal cortical development, which is responsible for modulating limbic regions of the brain associated with emotion and impulsive behavior [15, 53]. The practice of focused attention should strengthen the development of executive function and associated brain circuits for attention, inhibitory control, and awareness [43]. Research has shown that mindfulness is inversely associated with adolescent tobacco smoking behavior through its influence on negative affect and perceived stress mediators [5]. In a 2010 study, a 12-week school-based program of mindfulness-based cognitive therapy for children (MBCT-C) was shown to be feasible to implement and effective in reducing anxiety symptoms [44]. As additional studies using mindfulness-based interventions are proposed and tested for children and adolescents, there will be a need to rigorously assess intervention outcomes and ensure the fidelity of program implementation [23].

Mindfulness-based interventions may be particularly impactful as school-based programs to enhance self-regulation and coping and, importantly, improve school conduct and academic performance. Over the longer term, these interventions could sustain overall mental health and reduce the incidence of psychiatric disorders such as SUD [47]. More research, however, is needed.

Summary

Originally derived from practices of Buddhist religion to seek "awakening," meditative practices are being reexamined and interpreted in the context of psychology and neuroscience. Over the last several decades, research on, and application of, meditative practices to the treatment of various conditions such as SUD has become more common. This research revolution is providing valuable insight into how meditative practices modulate cognitive process and neurobiological mechanisms of the brain [20, 31, 33, 37].

While this approach may prove useful for the treatment of CUD, research has not adequately investigated this area. Research does suggest, however, that mindfulness-based interventions may be useful for treating SUD. In addition, these meditative practices may help patients cope with a variety of symptoms associated with CUD including craving, irritability, anger, depression, nervousness, and anxiety, as has been demonstrated for other SUDs and other psychiatric conditions [12]. Meditative practices may also provide an effective and appropriate substitute for marijuana use, by providing an alternative strategy for coping with stress and negative affect. Clearly, more research in determining the effectiveness of mindfulness-based treatment interventions for CUD is needed.

Finally, as a prevention strategy, mindfulness-based practices may be useful particularly for children and adolescents. During early stages of development, there is a growing capacity for cognitive control and self-regulation, which has been linked in part to maturation of the prefrontal cortex. Preliminary research suggests that children and adolescents are accepting of training in meditative practice when implemented in school-based programs. Meditative approaches may also have an immediate impact on cognitive ability such as attention and executive function, which could translate into long-term benefits in reducing a variety of risk behaviors, including substance use.

Overall, evidence for the use of mindfulness-based meditation for treating CUD is weak [21]. However, these approaches show promise for treating symptoms associated with CUD and SUD and may be important as part of drug abuse prevention strategies for children and adolescents. Importantly, the research on, and application of mindfulness-based practices to, psychiatric disorders is vibrant and maturing. Additional work is needed to determine the efficacy of this approach as treatment strategy for CUD.

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Cannabis Use Disorder Treatment and Reimbursement

25

Andrew M. Kiselica and Amy Duhig

Background

Many individuals perceive cannabis use to be relatively harmless, or even therapeutic, despite a lack of high-quality evidence to support these claims [1–4].[1] In fact, there is growing scientific consensus that recurrent cannabis use is harmful and that there is a true cannabis withdrawal syndrome that, along with other influences, maintains marijuana use over time [7–13]. Indeed, the American Psychiatric Association [14] recognizes persistent, difficult-to-control use of marijuana, despite frequent legal, health, and interpersonal consequences as cannabis use disorder (CUD) in its *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5).

Nearly six million people suffer from CUD in the United States [15]. These individuals are at increased risk for a number of negative outcomes. For example, they are more likely than individuals without CUD to experience mental health problems, like externalizing disorders and psychosis [16–18]. Moreover, prolonged marijuana use is linked with reduced cognitive functioning and cardiovascular and respiratory disease [19–21]. Finally, CUD has broader societal impacts, resulting in reduced achievement, increased healthcare utilization costs, and decreased employment [15, 16, 22–24].

Current treatment of this prevalent and harmful disorder is inadequate. There are currently no Food and Drug Administration (FDA)-approved pharmacotherapies indicated for CUD [25]. There are, however, a number of efficacious behavioral treatments. They include cognitive-behavioral, motivational interviewing, contingency management, and relapse prevention approaches. A meta-analysis of randomized controlled trials demonstrated a moderate overall effect size for these treatments—patients receiving an evidence-based psychotherapy fared better than 66% of individuals in the control conditions [26]. There is a dearth of evidence on the type of treatments offered/available to treatment-seeking individuals with CUD. Consequently, it remains unclear whether these evidence-based therapies are being accessed by patients. The existing evidence seems to point to the contrary: Most (87%) individuals with CUD do not participate in *any* treatment [15], let alone an evidence-based one. Furthermore, those that do seek treatment take significant time to reach out for help. The average adult seeking treatment for CUD has used marijuana for 10 years and attempted to abstain from use at least 6 times [27].

There are a number of explanations for this treatment gap. First, there are significant practical barriers to treatment access, such as a lack of treatment facilities in communities where they are needed [28]. Additionally, cannabis users often do not see a need for treatment or perceive a stigma associated with receiving treatment [29]. Such beliefs may reduce treatment initiation and/or adherence [30]. There may also be issues associated with reimbursement for CUD treatment services. The purpose of the current chapter is to review available literature on CUD treatment, access, and reimbursement. The chapter covers the following topics:

- Reimbursement for behavioral treatment of CUD
- Payer opinion on new pharmacotherapies for CUD
- Insights from other SUD treatment paradigms
- Future directions for researchers and drug sponsors

[1] Of course, it must be acknowledged that certain endocannabinoids have been reported to confer some health benefits when medically managed [5, 6].

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Reimbursement for Behavioral Treatment of CUD

Any discussion of reimbursement for services must start with a discussion of the costs of those services. Although specific data on CUD treatment costs are not available, SUD treatment in general tends to be quite costly. For example, in a survey of all SUD treatment providers in the state of Florida, median costs per average treatment episode ranged from $2528 to $28,096, depending on treatment type [31]. These high costs likely preclude out-of-pocket payment for care for most individuals with CUD, which has its highest prevalence in the lowest income groups [15]. Data from the National Survey on Drug Use and Health bears out this assumption [32]: The most commonly reported perceived treatment barriers are financial in nature (e.g., cannot afford treatment, treatment not covered by insurance).

High costs of treatment not only affect patients' ability to enter treatment but also influence provider decisions to offer treatment. As discussed above, treatments for substance use are often unavailable or inadequate. This lack of treatment offerings is concerning, given scientific consensus regarding the need for SUD treatment and its economic viability. There is general agreement that SUDs should be treated similarly to other chronic conditions, such as diabetes and heart disease, via multidisciplinary, multisystem, and long-term care recovery approaches [33]. Furthermore, there is a wealth of evidence to suggest that substance use treatment is cost-effective in that it reduces the need for more expensive treatments down the line due to the health harms associated with continued substance use. For example, multiple studies have demonstrated that individualized in-person therapies and internet-delivered interventions for CUD deliver benefits commensurate with their costs [34, 35]. Moreover, savings have been demonstrated on a population-based level: An analysis of Medicaid claims data from 2001 to 2008 found that substance abuse treatment yields a per member per month cost savings of $160–385, for an aggregated annualized estimate of $16.8 million per year [36]. Thus, SUD treatment appears medically necessary and financially responsible.

Why then are healthcare-providing institutions still reluctant to offer substance use treatment? One study of VA spending on SUD care by Humphreys and colleagues [37] provides a partial explanation. The authors reported that there was no evidence that spending on SUD treatment was associated with reduced costs for the providing institution that paid for the treatment. Thus, although SUD treatments appear to be cost-effective based on the benefits offered to the patient and the broader healthcare system, there is an economic disincentive for individual providers to offer these treatments.

Providers may also have difficulty obtaining reimbursement for substance use treatment services. Within the managed care system, there are a variety of current procedural terminology (CPT) codes available to clinicians seeking to receive reimbursement for SUD assessments and interventions [38]. These codes cover drug screening/testing, brief interventions, individual psychotherapy, group psychotherapy, family therapy, education and training for self-management, hospital and emergency department care, consultation, case management, and preventive medicine, among other services. Clearly, most behavioral treatments for CUD would fall into one or more of these categories.

But how do insurers currently manage requests made under these codes? Sterling and colleagues [39] conducted a review of the literature on access to treatment for adolescents with substance and co-occurring disorders. Herein, they summarized the current reimbursement landscape for substance use and mental health services in the United States (see also [40]). In integrated healthcare delivery systems, care is coordinated across substance use, psychiatric, and traditional medical departments. Such health plans often have prepaid, capitated, per-member reimbursement arrangements with service organizations, including cost-sharing features (e.g., deductibles and co-pays) to curb excessive spending. In contrast, health plans with less integration "carve out" reimbursement arrangements with specialized behavioral health providers, separate from other services. In these cases, the burden of cost saving is on the providers. Thus, private insurers typically reimburse for integrated services (in larger healthcare provision systems) or specialist services, outside of a larger or more traditional care setting.

Unfortunately, private insurers often provide little coverage for SUD treatments, resulting in much of the burden for reimbursement being shifted to publicly funded insurance options [39]. Indeed, individuals with private insurance are far less likely to receive treatment. For instance, an analysis of the National Survey on Drug Use and Health data showed that individuals with publicly provided insurance have 50–90% greater odds of receiving treatment relative to those with private insurance [41]. Regardless of its source, reimbursement is often insufficient to implement and deliver evidence-based SUD assessment and intervention options [42]. Healthcare spending patterns bear out this assumption: Although spending for mental health conditions has increased in recent years, spending for SUDs has not [43]. This trend is projected to continue through 2020, as spending on mental health and SUDs is expected to grow more slowly than spending on other health conditions [44].

Despite the expectation that spending on SUD treatment will remain insufficient, there is evidence that certain policy decisions will have a positive impact on SUD treatment

coverage. The most well-publicized of these policies at the federal level are the Paul Wellstone and Pete Domenici Mental Health Parity (MHPAEA) and Addiction Equity Act and the Patient Protection and Affordable Care Act (commonly called the ACA or Obamacare). These policies are expected to extend insurance coverage for SUDs in three ways: (1) by requiring that health plans and health insurers provide mental health and substance use benefits with the same limitations as those for medical/surgical benefits (this requirement is known as a mental health/substance use "parity law"), (2) by increasing health insurance coverage overall through subsidies and the extension of the age at which individuals can remain on their parents' insurance, and (3) by banning insurance companies from not providing coverage to individuals with preexisting conditions [45–47].

The full effects of the MHPAEA, ACA, and related state laws will not become clear for some time. In fact, they may never actually be realized—at the time of this writing, there is a push by Republicans to repeal the ACA (see, e.g., [48]). Nonetheless, some studies collected to date indicate that parity laws and the ACA have had a positive impact on SUD treatment coverage. For example, one research group conducted a study of state-level SUD parity laws using data from the National Survey of Substance Abuse Treatment Services [49]. The authors reported that implementation of any SUD parity law increased the treatment by 9% in specialty SUD treatment facilities. Saloner and colleagues [50] similarly found that the ACA provided coverage for an additional 10% of justice-involved individuals with SUD and an increase in Medicaid payments for SUD services (though not an increase in treatment rates). Finally, another research group examined SUD and mental health treatment expenditure data for high-risk children from a Federal Employees Health Benefits Program 2 years before and 2 years after implementation of the federal parity law [51]. They found that out-of-pocket costs were reduced by 5% (by $178) in this group. Despite these encouraging findings, some studies have suggested that parity laws have little to no effect on spending for SUD treatment services and do not result in significant changes in identification of SUDs, treatment initiation, or treatment engagement [52, 53].

To summarize, there is a significant unmet need for CUD treatment. Although several scientifically validated, moderately effective behavioral treatment options exist, most individuals with CUD do not enter treatment. Treatment is both expensive to the patient and the providing institution, creating significant practical barriers to effective intervention. Although providers can obtain reimbursement for their services, insurance companies often do not provide enough coverage for providers to remain viable, and much of the burden for reimbursement of SUD treatment has fallen on public insurers. Some state and federal policies have shown promise in expanding coverage and reimbursement for SUD treatment, though they appear to have had a limited benefit on actual treatment outcomes.

Pharmacological Treatment of CUD

Although behavioral interventions for CUD often do not reach those that need them, at least they exist as treatment options. As discussed above, there are no FDA-approved pharmacological interventions for CUD. Consequently, medical providers are left to treat co-occurring conditions (e.g., chronic pain, depression, etc.) in the hopes of influencing CUD symptoms indirectly. Lack of investment in this treatment area may result from a number of factors. First, as has been seen, CUD is rather difficult to treat. Consequently, investors may be discouraged by an anticipated lack of success from funding new treatment endeavors. Second, the upfront costs of reaching initial FDA approval are quite high, with estimates ranging from $1 to $11 billion [54]. Moreover, returns on investments may not be seen until following the approval process, after the additional costs of marketing and distributing a drug have been accrued. Third, drug sponsors may be wary of forging into a new area when it is unclear how a novel pharmacotherapy for CUD will be assessed, managed, and reimbursed by managed care payers. Fourth, sponsors may be unclear about how to appropriately design clinical trials to test potential pharmacotherapies.

These first two concerns can only be overcome by intrepid investors and sponsors, capable of accumulating a great deal of capital and demonstrating the patience and business acumen to realize long-term profits in a novel market with vast earning potential. However, the final two concerns may be addressed by scientific and marketing studies involving payers. One such study was recently conducted by Kiselica and colleagues [55] and will be discussed in detail below.

These researchers conducted a survey with 50 managed care payers. The study had four goals: (1) to determine the extent to which payers view an unmet need for CUD treatments, (2) to assess payers' knowledge of CUD treatment endpoints, (3) to determine the most appropriate endpoints and populations for CUD treatment research, and (4) to examine the likelihood of a quick review of novel pharmacotherapies for CUD.

Results were encouraging for companies looking to develop CUD interventions. First, most (70%) payers rated the unmet need for new pharmacotherapies for CUD as at least moderately important. Thus, drug sponsors can be reasonably confident that payers would be unsurprised by the introduction of new CUD treatments. Second, the majority of payers (62%) reported that they were at least moderately familiar with CUD treatment endpoints. Consequently, drug

sponsors would not bear an undue burden in educating payers about the results of their trials. Third, payers rated abstinence and decreased resource utilization as the most important endpoints to be included in CUD treatment trials. Furthermore, they suggested that individuals with co-occurring disorders should be the focus of treatment efforts. Knowing these preferences could allow drug sponsors to design studies that are specifically geared toward meeting the needs of payers. Finally, most participants said an FDA-approved CUD treatment would be formally reviewed by payers within 6 months (58%) or a year (36%), suggesting that novel treatments could quickly be placed onto formularies and be available for reimbursement.

These results provide encouragement and guidance to sponsors considering development of pharmacotherapies for CUD. Of course, the study was limited in several ways, leaving avenues for future research. First, the study focused on payers' current perceptions of future CUD treatments. Such perceptions may not translate directly into real-world decisions. Future research may longitudinally explore the relationship between a priori payer perceptions and eventual formulary/reimbursement decisions. Second, the study only informs us about payer opinion on potential CUD treatments and does not provide insights into how the FDA, providers, and patients may receive a new pharmacotherapy. Subsequent studies may replicate Kiselica and colleagues' work with other stakeholders. Finally, the results did not provide information about the market viability of a new pharmacotherapy. Consequently, pharmacoeconomic studies are needed to establish the financial feasibility of a new drug to treat CUD.

In summary, there are no FDA-approved pharmacotherapies for CUD. Drug sponsors may be reluctant to enter this landscape for a number of reasons, including that they are unsure how managed care payers will receive new treatments. The study by Kiselica and colleagues suggests that most payers see an unmet need for new pharmacotherapies and that they are capable of quickly and effectively evaluating new treatments. Nonetheless, longitudinal and market access research are necessary to provide greater certainty that a CUD pharmacotherapy would be approved and become a commercial success.

Approval and Dissemination of a CUD Pharmacotherapy: Insights from Naltrexone

Clearly, more research is needed to inform the creation and marketing of a new CUD pharmacotherapy. Prior to the conduct of this research, one can gain insights on the potential for a CUD treatment by studying pharmacotherapies for other SUDs. Naltrexone was the second FDA-approved medication for treating alcohol use disorder (AUD). It provides a solid case example for entry into the SUD treatment landscape, from which one can draw inferences about the likelihood of success for a CUD pharmacotherapy. The history of naltrexone's approval and commercial introduction points to a slow process of large-scale acceptance and utilization but long-term commercial success.

Strain provided a review of naltrexone, its approval, and use in his 2010 book [56]. Naltrexone is an opioid receptor antagonist, originally developed in the 1960s to treat opioid addiction. It functions by blocking the reinforcing effects of opioids, thereby reducing the likelihood of continued drug use. In the 1980s, it was discovered that naltrexone has a similar effect on alcohol. Subsequent clinical trials demonstrated that it is effective at improving abstinence and reducing alcohol use among individuals with AUDs, leading to eventual FDA approval for this purpose in 1995. The history of naltrexone makes clear the lengthy process of drug approval in a new disease state. In this case, it took over 30 years from the development of naltrexone until its approval for the treatment of AUDs.

Following approval, naltrexone met with success in obtaining coverage and reimbursement through health plans. Both branded naltrexone (trade name ReVia) and generic naltrexone were likely to be covered by private health plans in 2003—93% of plans covered the branded version vs. 94% of plans for the generic option [57]. Moreover, more recent analyses of private health plan data indicate that coverage has reached nearly 100% [58]. However, branded naltrexone is likely to receive more costly management strategies and be placed on the third tier of the formulary [57, 58].

Public Medicare and Medicaid plans have demonstrated similarly widespread coverage of naltrexone, with plan coverage for generic naltrexone reaching 100% by 2013 [59, 60]. Limitations are rare under these plans, with generic naltrexone typically being placed on tier one and receiving restrictions in less than a quarter of plans [59, 60]. Consequently, under public plans, costs to the patient for generic naltrexone are rather low, ranging from $3 to $50 per month on average, depending on coverage options [59]. Of course, management of branded naltrexone is more strict and more costly to the patient. The widespread acceptance of naltrexone by the insurance industry suggests that a pharmacotherapy for CUD could meet with similarly broad formulary acceptance and unrestrictive management, especially after the introduction of generic alternatives.

Despite the widespread acceptance of naltrexone in the insurance industry, utilization of the drug has been disappointing since approval. Similar to CUD, treatment of AUDs is sporadic at best, with only about 14.6% of individuals with an AUD receiving treatment [61]. Consequently, most of the naltrexone-eligible population never receives the option to obtain the drug. Among the small treatment-seeking

population, use of oral naltrexone (the original formulation) is rather low—<10% according to one analysis of a large claims database [62].

This disappointing utilization of naltrexone may be explained by several factors. First, meta-analyses suggest that it only has a small effect on alcohol-related outcomes when compared to placebo [63]. Given this data and the possibility of limited perceived success among real patients, providers and patients may have been unlikely to prescribe and use naltrexone. Second, there is a clear preference to offering and using behavioral interventions for alcohol [64]. Third, there may be a lack of available prescribing providers [64].

These explanations for poor utilization of naltrexone highlight several ways in which a CUD pharmacotherapy could be more successfully distributed. First, the drug would need to show moderate-to-strong effectiveness to encourage its use. Second, efforts would need to be made to increase awareness and acceptance of medical options for CUD interventions. Third, prescribing practitioners would need to be trained and incentivized to work in CUD treatment facilities. These latter two changes are likely not unique to CUD treatment but necessary to improve SUD treatment more broadly.

Beyond these large-scale efforts, research has suggested several specific institutional and policy factors that may increase adoption and sustainability of naltrexone among providing institutions. On an institutional level, some of these factors included use of prescription drugs, possession of an employee handbook, receipt of accreditation, receipt of revenues from private insurance, receipt of referrals from the criminal justice system, and hiring of larger numbers of medical staff [65, 66]. In contrast, organizations using a 12-step model and more experienced administrators were less likely to implement use of naltrexone [66]. On a government level, policies that encourage the use of generic drugs and lower drug costs are associated with increased likelihood of naltrexone adoption [67]. On the other hand, state efforts restricting access to pharmaceutical technologies, limiting access to pharmacy networks, and imposing limitations on use of Medicaid benefits for substance abuse treatment are linked with lower likelihood of naltrexone adoption [67].

These findings may be extended from naltrexone to understand how best to promote a new CUD pharmacotherapy. Greater acceptance of such a drug might be achieved by encouraging providing organizations to make professional improvements (e.g., accreditation, acceptance of private insurance, abandonment of practices without an evidence base). Furthermore, government agencies may help by engaging in efforts to expand use of generic drugs and lower drug costs.

Though improvements in naltrexone acceptance and persistence can clearly be made, this drug is far from a commercial failure. Data from 2002 to 2007 of the IMS National Prescription Audit Plus reveal sales averaging over $20,000,000 per year for oral naltrexone [68]. Thus, even if low rates of use are seen with a new CUD pharmacotherapy, a drug sponsor may still expect high rates of return on drug sales. Consistent sales of naltrexone may in part reflect data suggesting that it reduces overall treatment costs [69, 70]: Once providing organizations began offering naltrexone and managed care organizations began reimbursing for it, they continued to do so on the basis of net economic gains. Thus, sales of a CUD treatment drug might be supported via cost-effectiveness studies.

Importantly, oral naltrexone appears to have paved the way for other commercially successful alcohol treatments. Indeed, while sales of naltrexone remained relatively stable, newer formulations (i.e., injectable, extended-release naltrexone) and alternative molecules (i.e., acamprosate) have seen increasing sales for the treatment of AUDs [68]. Moreover, as evidence supporting medication-assisted treatment of AUDs builds, there has been an increase in use of AUD medications in some sectors. For example, within the VA system, which is particularly adherent to evidence-based guidelines, there has been a slight increase in the receipt of medications for AUD [71]. Thus, once a CUD pharmacotherapy enters the market, there is opportunity for a drug sponsor to build evidence for its product, leading to an increase in utilization.

Though there is little data on the potential of new pharmacotherapies for CUD, insights can be drawn by studying the historical and empirical data on drugs for other SUDs. This section included a review of naltrexone as a treatment for AUD. This review suggested that there are significant practical barriers to the approval and dissemination of a new pharmacotherapy, which may result in a significant time lag to realizing profits. Nonetheless, analysis of naltrexone suggests there is opportunity for widespread coverage and reimbursement of a CUD treatment, as well as long-term commercial success with the opening and expansion of a new market.

The Future of CUD Treatment, Research, and Policy

As previously discussed, there are a number of moderately effective behavioral therapies for treating CUD. Evidence from other SUDs suggests that adding a pharmacotherapy to these interventions might improve patient outcomes in a cost-effective manner [69, 72, 73]. There are several pharmacotherapies in Phase III development for this purpose according to clinicaltrials.gov. They include N-acetylcysteine, nabilone, buspirone, and lofexidine + Marinol, as well as a number of drugs designed to treat comorbid psychiatric and medical conditions, in addition to CUD.

For these agents to become treatment and commercial successes, they need to achieve several goals. First, they must show efficacy in treating CUD symptoms and associated harms, as well as adequate safety. The long line of treatments now available for tobacco, alcohol, and opiates indicates that this goal is manageable. Further clinical trials, open-label extensions, and aftermarket studies of CUD pharmacotherapies will hopefully lead to FDA approval and public dissemination.

Second, CUD treatment drugs will need to be received well by the medical and patient communities in order to be prescribed and taken. Consequently, drug sponsors will need to conduct studies of value-based messaging and undertake aggressive marketing campaigns. However, even when evidence for an SUD pharmacotherapy is strong and the medical community and public at large are convinced of its value, rates of uptake can be quite low due to significant practical barriers. Thus, government and organizational support will be needed to improve access to treatment by increasing the number and quality of substance use facilities, training prescribing providers in CUD management, and reducing stigma associated with obtaining treatment.

Third, CUD pharmacotherapies will need to be adequately covered and reimbursed to facilitate patient access. The widespread coverage of naltrexone suggests that this goal is attainable. Furthermore, preliminary research with payers indicates that insurers see an unmet need for a new pharmacotherapy for CUD and are educated enough to quickly make formulary and reimbursement decisions on new products. Thus, if a CUD pharmacotherapy is safe and efficacious, it should meet with adequate acceptance from the managed care community.

Finally, once a CUD treatment is widely reimbursed, logistical support will need to be put into place to ensure adoption and sustainability. Governmental organizations can create policies that encourage access to drugs and reduce drug costs. Furthermore, providing organizations can implement practices that encourage adherence, such as case management and treatment of comorbid conditions.

Summary

CUD is a prevalent, costly, and harmful condition. Most individuals with CUD do not obtain treatment. There are a number of scientifically validated, moderately effective behavioral treatments for CUD. However, practical barriers and inadequate insurance coverage often preclude participation in these programs. Unfortunately, no FDA-approved pharmacotherapies exist to supplement available behavioral treatments. Research with payers and investigations of other SUD treatments entering relatively open markets indicate potential for the development of CUD treatment drugs. Specifically, insurance coverage and reimbursement of new drugs are likely, though adoption and persistence of such drugs in the market may be more problematic. It is likely that a new pharmacotherapy for CUD will be approved in the next few years.

Consequently, there may be a need for policy and organizational efforts that encourage access to low-cost drugs and training of medical providers in CUD management to facilitate CUD treatment dissemination.

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International Aspects of CUD

26

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Abbreviations

AIHW	Australian Institute of Health and Welfare
APA	American Psychiatric Association
APAIC	Asia and Pacific Amphetamine-Type Stimulants Information Centre
CAST	Cannabis Abuse Screening Test
CICAD	Inter-American Drug Abuse Control Commission
CUD	Cannabis use disorder
CUDIT-R	Cannabis Use Disorder Identification Test—Revised
DAINAP	Drug Abuse Information Network for Asia and the Pacific
DALYs	Disability-adjusted life years
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECOWAS	Economic Community of West African States
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
ESPAD	European School Survey Project on Alcohol and Other Drugs
EU	European Union
GBD	Global Burden of Disease
GSHS	Global Student Health Survey
ICD-11	International Classification of Diseases, 11th Edition
LMIC	Low- and middle-income countries
MENA	Middle East and North Africa
MOH	Ministry of Health
NDSHS	National Drug Strategy Household Survey (Australia)
NIDA	National Institute on Drug Abuse
NPS	New psychoactive substances
NZHS	New Zealand Health Survey
PICT	Pacific Island countries and territories
SACENDU	South African Community Epidemiology Network on Drug Use
SBIRT	Screening, brief intervention, and referral to treatment
SJU	Standard Joint Unit
SMART	Global Synthetics Monitoring: Analyses, Reporting and Trends
THC	Tetrahydrocannabinol
UNODC	United Nations Office on Drugs and Crime
WENDU	West African Epidemiology Network on Drug Use
WHO	World Health Organization
YRBS	Youth Risk Behavior Study

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Globally, cannabis is the most frequently used illicit drug—about 183 million people aged 15–64 used cannabis at least once in 2015, or 3.8% of adults. Prevalence varies between 1.8% in Asia and 10.3% in Oceania. Cannabis use also is the most frequent cause of seeking drug treatment, accounting for 39% of global treatment requests. Globally, the average

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age of people seeking treatment for cannabis use disorder (CUD) is 24. CUD is the most prevalent drug use disorder in Australia, Canada, and the United States (excluding alcohol and tobacco). Globally, an estimated 13.1 million people suffer from CUD, while 29.5 million individuals suffer from any drug use disorder [50, 65].

Reliable data from low- and middle-income countries (LMIC) are not generally available, so it is difficult to know if the higher prevalence rates in higher income countries are a result of increased use or better data collection. New approaches, standardized data collection tools, and continuous monitoring are needed [50, 65]. A 2011 study found qualitative evidence of cannabis use or dependence in 201 of 229 countries and territories; however, only 95 countries estimated prevalence of cannabis use, and only 7 countries—Australia, Canada, Germany, India, New Zealand, the United Kingdom, and the United States—estimated prevalence of cannabis dependence. The authors found the least data on cannabis use prevalence in low-income countries from Oceania, North Africa, the Middle East, sub-Saharan Africa, and Asia, where only 13 of 128 countries or territories collected data between 2000 and 2008 [17]. In the United Nations Office on Drugs and Crime (UNODC) database for 2009 to 2015, only 19 of those same 128 countries or territories reported adult cannabis use prevalence data, and just 16 of the 128 countries reported youth cannabis use prevalence data [52, 53]. Much of this data comes from household or school surveys, which do not capture vulnerable populations such as homeless people, those in institutions, and youth not in school. Moreover, cultural norms, fear of legal consequences, or respondents' suspicions about anonymity and confidentiality may suppress honest responses [16, 17]. Survey methods and definitions vary within and among countries, also complicating international comparisons.

Defining and Diagnosing Problematic Cannabis Use

The definition and identification of CUD depend on the diagnostic criteria adopted. In 2013, the American Psychiatric Association released the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) to update the diagnostic system used in research and clinical practice [3]. The most significant change in DSM-5 substance abuse classifications from previous versions was to replace the separate classes of substance abuse and substance dependence with a single class—substance use disorder—that is further characterized as mild, moderate, or severe. Individuals must have at least 2 of 11 criteria to be diagnosed with a substance use disorder [33]. In May 2018, the World Health Organization (WHO) is scheduled to release the 11th revision of the International Classification of Diseases (ICD-11), which serves as a global tool for clinical diagnosis and collection of health statistics [22, 24, 44, 63]. A draft version is available online (https://icd.who.int/dev11) to facilitate comments, revisions, quality control, translation, and field-testing [24, 44, 63, 64]. Unlike DSM-5, the draft ICD-11 keeps separate categories for harmful use (abuse) and dependence but changes the diagnostic criteria for both categories. For dependence, diagnostic criteria were reduced from six to three—tolerance, time spent, and impaired control—with at least two criteria required for a diagnosis. For harmful use, the four diagnostic criteria of the previous version have been reorganized, with family harm added to failure to fulfill major obligations, legal problems, and use in hazardous situations. One of the four criteria is required for a diagnosis of harmful use [15, 33, 44].

Several recent studies have compared the similarities and differences in cannabis use or dependence diagnoses using the DSM-5 and ICD-11 definitions. A general population survey of Australian adults that assessed disorders using the WHO World Mental Health Composite International Diagnostic Interview found that the DSM-5 lifetime prevalence of any CUD was 28.1% (95%CI, 24.8–31.3) compared to the ICD-11 prevalence of 30.9% (95%CI, 27.7–34.1). Using the ICD-11 definition of dependence correctly identified individuals with a long history of use, co-occurring disorders, and related social problems, but using the DSM-5 definition identified more people with less severe symptoms [33]. In contrast, a study of 339 14–18-year-olds undergoing outpatient treatment for addiction in the United States found that ICD-11 identified a significantly higher prevalence of dependence than using the DSM-5 definition for moderate or severe dependence ($p < 0.01$). There were 27 adolescents who met the ICD-11 criteria for dependence, but not the DSM-5 criteria; these individuals were most likely to report symptoms related to tolerance (92.6%) and time spent (81.5%), but not the more severe symptom of impaired control. Of the 339 study participants, there were just 9 adolescents who met the DSM-5 criteria for moderate or severe use but not the ICD-11 criteria. All reported symptoms related to role impairment and interpersonal problems; 77.8% also reported hazardous use [15].

Further research must determine if the differences between DSM-5 and ICD-11 prevalence rates are due to differences between the two systems' criteria or differences among the studies' populations, treatment status, or assessment instruments. Lago and colleagues [33] suggest that DSM-5 definitions may be most applicable in high-resource countries where early interventions exist for individuals with less severe symptoms. Chung et al. [15] warn that the differences between DSM-5 and ICD-11 will affect how the systems are used in practice to identify treatment needs among specific populations. Another review suggests that neither the DSM-5 nor the ICD-11 allows for individual differences in etiology and treatment response for individuals with substance use and co-occurring disorders [24].

Treating Problematic Cannabis Use

Demand for problematic cannabis use treatment is increasing in high-income and some LMIC [65]. Between 2006 and 2014, the rate of Europeans first seeking treatment for cannabis use increased by 50%. The vast majority (80%) were younger than 34 years [50]. Data from the United States and Europe document rapid increases in the potency of cannabis since 2006, with the average percentage of Δ9-THC content rising to well over 15% [19, 49]. UNODC notes the association in increases in cannabis dependence and DSM-5 disorders with the availability of higher-potency cannabis products but adds that some of the increased demand for treatment is a result of newly available treatment services and improved access to treatment in developed countries [50]. In the Canadian province of Ontario, one-third of patients admitted to publicly funded treatment facilities were seeking treatment for CUD [28].

Evidence-based treatment for cannabis use is limited to behavioral and psychosocial interventions, with no approved pharmacotherapy. CUD treatment infrequently addresses co-occurring disorders or polysubstance use, despite the fact that 40–80% of individuals receiving drug abuse treatment have been diagnosed with polysubstance use [50]. Several US studies have found limited evidence on the effectiveness of screening, brief intervention, and referral to treatment (SBIRT) interventions for cessation or use reduction among individuals who use cannabis but are not dependent [42, 43, 45, 61]. Much more research is needed in a variety of cultural settings, as a binational study by Harris et al. [27] demonstrates. The study, conducted at ten sites in the Czech Republic and nine sites in the United States, found differing results in the two countries. In the United States, the intervention significantly reduced alcohol use or initiation, but the effect on cannabis use cessation, reduction, or initiation was not significant. In the Czech Republic, the same brief intervention had little effect on alcohol use but significantly reduced cannabis use among Czech adolescents both during the intervention and at 3 months (5.5% vs. 9.8%, aRRR = 0.37, 0.17–0.77) and 12 months (17.0% vs. 28.7%, aRRR = 0.47, 0.32–0.71). At the 12-month follow-up, initiation of use was also reduced (5.2% vs. 0.9%, aRRR = 0.22, 0.05–1.04). More research is also needed on implementing SBIRT in nonmedical settings. A recent school-based SBIRT intervention in ten Wisconsin sites found that 46.1% of students who used cannabis reported that they intended to reduce use following the intervention. Intention to initiate cannabis use also decreased (mean = 5.7/7) among students who were either ambivalent about initiating cannabis use or reported high intentions to initiate use [36].

Bonn-Miller et al. [9] report that a three-question version of the Cannabis Use Disorder Identification Test—Revised (CUDIT-R) may reduce time and training barriers to cannabis screening in clinical settings. Most CUD treatment research has been conducted in high-income countries, primarily Australia, Germany, the Netherlands, New Zealand, and the United States. That research has demonstrated the effectiveness of psychosocial interventions including cognitive behavioral therapy, contingency management, motivational enhancement therapy, and psychosocial problem-solving therapy [28, 50, 65].

Assessing the Global Impact of Problematic Cannabis Use

Globally, deaths and disability-adjusted life years (DALYs) associated with CUD remain small, especially when compared to other substance use such as tobacco, alcohol, or opioids. The 2015 Global Burden of Disease study reports no deaths attributed directly to CUD and a tiny 5.3% increase in CUD-related DALYs between 2005 and 2015 [23]. Recent reports, however, indicate increased awareness of CUD-associated harms identified through new research. Canadian researchers found that in 2012 cannabis was associated with 287 deaths and more than 66,000 DALYs, primarily among young men [28]. Another Canadian study analyzed 2012 traffic collisions attributed to cannabis use and documented 75 fatalities, more than 4400 injuries, and more than $1 billion Canadian in property damage [58]. A growing body of research is documenting the association between cannabis use and self-harm or suicidal ideation, attempts, and deaths [10, 26]. Synthetic cannabinoids have been linked to deaths, adverse health effects—including severe incidents such as seizures, psychosis, chest pain, breathing difficulties, and loss of consciousness as well as symptoms such as vomiting, drowsiness, agitation, hot flushes, dilated pupils, and dry mouth—and withdrawal [50].

Synthetic cannabinoids accounted for nearly one-third of new psychoactive substances (NPS) identified in December 2016. As with most NPS, synthetic cannabinoids vary widely in pharmacology, toxicity, potency, quality, effects, and duration of action, although they all mimic the effects of natural cannabis. A few studies indicate that users of both synthetic cannabinoids and natural cannabis prefer the natural product [50].

Globally, the legal status of cannabis use is changing. Uruguay legalized marijuana in 2013, and Canada announced plans to legalize marijuana by 2018, although neither the Uruguayan nor the Canadian laws had been fully implemented near the end of 2017. In the United States, marijuana is illegal at the Federal level but legal for recreational use in eight states and the District of Columbia. Eight other nations plus 29 US states and the District of Columbia permit use of cannabis for medical purposes [32]. These changing regulatory environments provide the opportunity for natural

experiments, but data to date remain inadequate for detailed analysis. Some researchers have suggested guidelines to reduce the risks of cannabis use [21], establish regulatory guidelines [41], or develop new types of data to better analyze the effects of policy changes [57].

Factors Affecting Data Quality

Epidemiological research is complicated by difficulties in determining the form, quantity, and content of the cannabis consumed. Recent research supported by the Spanish Ministry of Health Plan Nacional Sobre Drogas proposes adopting a "Standard Joint Unit (SJU)" comparable to the standard drink unit used in alcohol research [13]. The authors conclude that the SJU should be set at 7 milligrams of THC and argue that the wide variety of THC content in different cannabis strains is similar to the wide variety of alcohol content in different liquors.

Improving Data Quality

Quality data that capture cannabis use, products, intensity, and trends, and document the health, social, and economic effects of short- and long-term use are needed to better characterize CUD globally. This quality data is necessary to help countries provide adequate treatment and prevention services and develop evidence-based drug policies. There are significant knowledge gaps in these areas, however, from monitoring through neurobiology, clinical, observational, prevention, health policy, health economics, public health, and public safety research. Lack of funding, infrastructure, and research capacity are major barriers to acquiring such needed data. Additionally, international drug control treaties and national regulations restrict some research. Priorities for future cannabis research include development of regular, population cohort studies of cannabis use with standardized questionnaires that measure the type of cannabis preparation used, THC and other cannabinoid strength, amount smoked or consumed, frequency and duration of use, demographic characteristics of users, and patterns of harmful use and dependence. Factors that moderate or enhance risks for problem cannabis use, relapse, or use of other substances must be better understood. Studies also should assess the usefulness of school surveys for estimating cannabis use among all young people [38, 65].

Countries should be encouraged to use standard surveys or incorporate core questions into existing country-specific surveys and to harmonize data collection to improve comparability. International organizations should develop guidelines for data collection methods, standards for research methods and study design, uniform terminology, and evidence-based question banks. More research also is needed to determine the effects of increased availability of cannabis, whether through recreational or medical use, on risk perception and use patterns. Additionally, studies must elucidate the relationship between THC content and changes in use, treatment demand, and adverse health effects [38, 65].

There is little conclusive evidence about the health effects of cannabis or cannabis derivatives, and research is required to document their therapeutic and adverse health effects. Studies should examine the association between cannabis use and cancer, heart disease, stroke, diabetes, respiratory illness, immune function, injuries, death, psychosocial problems, mental health, other substance use, and prenatal, perinatal, and postnatal outcomes. Rapid, accurate, and noninvasive diagnostic tools must be developed to assess cannabis impairment [38].

Aspects of Cannabis Use by Global Region

Africa About 7.5% of African adults use cannabis, and more Africans seek treatment for cannabis use than any other substance [50]. Many African countries do not have recent prevalence estimates. UNODC Statistics Online [52] includes annual prevalence data on cannabis use by adults 15–64 from just 15 of 55 African nations: The most recent report is 2.6% from Tunisia in 2013; the oldest is 17.7% from Zambia in 2003. Algeria reported the lowest annual adult cannabis use prevalence—0.52% in 2010—and Zambia the highest.

The data on lifetime prevalence among youth is equally scant and divergent: A total of 14 nations report some data about youth, but cross-national comparisons are complicated because countries define youth differently, assess different time periods (lifetime, past year, or past month), and inquire about different forms of cannabis (resin, herb, or both). The most recent youth prevalence reported is 9.30% from Namibia in 2015; the oldest is 11% from Ethiopia in 1999. The highest youth lifetime prevalence rate is 35.3% from Zambia in 2004; the lowest is 0.17% from Algeria in 2010 [53]. A 2013 study of Egyptian secondary school students found that only tramadol was used more frequently than cannabis [50]. Egypt also reports the highest demand for cannabis among the Arab states [54].

Since 1996, the Medical Research Council of South Africa has supported a robust drug use epidemiology network that meets twice each year to monitor substance use, review policy implications of emerging trends, and identify issues that require additional research. In June 2017, the South African Community Epidemiology Network on Drug Use (SACENDU) reported that cannabis is the primary or secondary drug prompting people to seek treatment, particularly among patients younger than 20 [47].

Following a March 2017 ruling by the Western Cape provincial high court that the country must change national laws to permit personal use, possession, and cultivation of marijuana at home, SACENDU suggested researchers investigate why cannabis users seek treatment, the health consequences of smoking illicit drugs, and the impact of the court ruling on young peoples' risk perceptions and use of marijuana.

Recent peer-reviewed studies from Africa tend to be small, such as a literature review exploring the consequences of substance use among high school students in Ethiopia [1]; Nigerian prevalence estimates among patients at a psychiatric hospital [2] or prison [48]; and data from a Botswana drug treatment center [46] or university [35].

Efforts are underway to improve statistically useful data collection, however. The EU, UNODC, Africa and Middle East Congress on Addictions, International Society of Addiction Journal Editors, and International Brain Research Organization African Centers for Advanced Training in Neuroscience all support capacity building efforts in the region. The West African Epidemiology Network on Drug Use (WENDU) is a joint EU/UNODC program operating in the 15-member Economic Community of West African States [18, 51]. By late 2017, WENDU had held workshops in Côte d'Ivoire, Liberia, Nigeria, and Senegal to harmonize drug abuse epidemiology data collection tools and promote adoption of evidence-based prevention and treatment interventions in the region [51].

Asia, Near East, and Middle East Although cannabis is produced throughout the region, only about 1.8% of adults 15–64 use cannabis, far below the global prevalence of 3.8% [50]. For countries in one segment of the region—the Near East, the Middle East, and Southwest Asia—the adult cannabis prevalence is 2.7%, higher than the region as a whole, but still lower than the global prevalence rate [52].

In addition to limited resources, national surveys on drug use are impeded in this region by challenges related to population size, geography, literacy, communications, cultural norms, and legal penalties for drug use or possession [16, 17]. Data are particularly scarce in the countries with the largest populations: Bangladesh, China, and India [16]. UNODC Statistics Online [52] includes prevalence data on cannabis use by adults 15–64 from 28 of 48 Asian countries. There are no national prevalence estimates for adult cannabis use in China, although 2003 reports are included from the Chinese territories of Hong Kong and Macao. The most recent and lowest prevalence is 0.18% from Indonesia in 2015; the highest prevalence is 8.88% from Israel in 2009; and the oldest prevalence data are 2003 reports from Armenia, Cambodia, Malaysia, and Uzbekistan [52]. Of 29 countries reporting, about 25,000 people in Asia were seeking treatment for CUD in 2015, compared to 675,000 in treatment for opioid use and 500,000 being treated for amphetamine use [50].

As in Africa, youth prevalence reports are complicated by different definitions of youth, time periods, and forms of cannabis. The most recent lifetime prevalence reports are 2015 date from Georgia at 11% and Indonesia at 0.59%. The oldest youth lifetime prevalence data are 2001 reports from Bangladesh at 5% and Kyrgyzstan at 0.3%. The highest lifetime prevalence report is from Kazakhstan at 11.2% in 2012; the lowest is 0.1% from Korea in 2006 [53].

Many peer-reviewed studies of adult cannabis use prevalence focus on arrests and seizures. In Japan, about 19.3% of drug-related arrests in 2008 were attributed to cannabis, more than 2.5 times the percentage of cannabis-related arrests reported in 2001 [30]. In Korea, cannabis has been second to methamphetamine in terms of seizures and arrests, but new psychotropic substances may be overtaking cannabis [20].

Since 2000, UNODC has instituted several drug abuse monitoring efforts in the region, such as the Asia and Pacific Amphetamine-Type Stimulants Information Centre (APAIC), Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART), and the web-based Drug Abuse Information Network for Asia and the Pacific (DAINAP), but their primary focus is not cannabis [16].

Europe The 28 EU member countries share a long-established, standardized monitoring system that provides an overview of cannabis use in Europe. Considerable heterogeneity remains between EU countries participating in routine drug monitoring, both in terms of their national drug situations and in respect to their capacity to report on it [25]. Quantitative data, together with annually updated national country overviews, can be found at http://www.emcdda.europa.eu.

Unlike cannabis consumption patterns elsewhere, European cannabis is commonly smoked mixed with tobacco. Historically, imported cannabis resin has been the dominant form of the drug in much of Europe, but that is changing with recent, intensive cultivation of herbal cannabis within the region. Although more drug seizure operations now involve herbal cannabis, the volume of resin seized still remains larger, probably because resin is more vulnerable to interdiction. As domestic herb producers introduced high potency strains of cannabis (meaning high concentrations of Δ9-THC, the main psychoactive component of cannabis), resin producers also switched to more potent strains of the plant. Cannabis potency for both herbal and resin forms of the drug has increased in the medium term: between 7% and 11% (range 3–22%) for herbal cannabis and 11–19% (range 4–28%) for resin in 2015. Increased potency and the regular use of cannabis with tobacco are both likely to elevate the health risks associated with cannabis use.

Epidemiological data do not currently permit the direct measurement of either the incidence or prevalence of CUD at the European level, nor is this possible to any great extent from the available national data. Although somewhat limited, self-reports of cannabis use and help-seeking behavior provide an indirect measure of problem cannabis use, trends over time, and meaningful comparisons between countries after adjusting for methodological differences. Most countries use general population and youth surveys to collect a core set of standardized data—including lifetime, last year, and last month prevalence of cannabis use—but may not collect data annually or use different time periods and recruitment procedures.

Across Europe, based on the most recently available data, an estimated 26% of the adult population (ages 15–64) used cannabis in their lifetime; national estimates varied between 4% and 41%. An estimated 7% of adults used cannabis in the last year (range 1–11%). The estimated last month prevalence was nearly 4% (range 0.7–7%), around 13 million people. These estimates increase considerably among younger cohorts: For those aged between 15 and 34 years, lifetime, last year, and last month estimates are 35%, 14%, and 8%, respectively.

A subset of 23 countries also estimates daily—or nearly daily—use, suggesting that around 1% of the European adult population uses cannabis daily. Around 30% of daily users were over 30 years of age and three-quarters were male.

Estimates of daily use are likely to provide the best proxy indicator of CUD, but they need to be interpreted with caution: The numbers reporting daily use are often very low; important national differences may exist in response level biases; and there is no consensus on the proportion of daily users who would receive a CUD diagnosis. Thus, the most practical, achievable method for estimating CUD prevalence in Europe would be to calculate the likelihood that those reporting monthly or daily cannabis use would also receive a CUD diagnosis. Some recent research investigated the development and use of short assessment tools in population surveys to improve identification of cannabis use problems [34]. The Cannabis Abuse Screening Test (CAST) has not been implemented in sufficient countries to estimate CUD, and including an assessment instrument in all surveys may not be feasible due to practical, cost, and methodological concerns.

Since 1995, the European School Survey Project on Alcohol and Other Drugs (ESPAD) has collected data at 4-year intervals about cannabis use among school students aged 15–16 in about 40 countries (http://www.espad.org). Not all countries participate in each wave of the project, and the absence of Germany, Spain, and the United Kingdom in the last round limits its usefulness in providing a comprehensive European overview. In addition to monitoring alcohol, tobacco, and other drug use, ESPAD assesses behavioral and other problems, which helps elucidate the association between substance use and problematic behavior. Levels of reported cannabis use among students in EU member states and Norway have been stable since the mid-1990s. Most recently, lifetime prevalence of cannabis use among boys and girls was around 21% and 16%, respectively. Past month prevalence was 9% and 6%. Only 2% of students reported using cannabis on more than nine occasions in the last month.

Methodological issues increasingly make collecting survey data using established approaches more challenging in Europe. Because they tend to catch relatively small numbers of those reporting intensive cannabis use, population-level samples are of limited analytical utility. Focused studies and Internet-based surveys targeting regular cannabis users have generated interesting findings, but they are not representative and thus far have not added to knowledge about CUD within Europe.

EU nations routinely collect data on new treatment demands and on all clients first entering treatment in the reporting year, a proxy for incident cases. Treatment demands attributed to cannabis use statistically increased between 2003 and 2014, rising from 43,000 in 2006 to 76,000 in 2015, and cannabis is the most commonly mentioned drug for new attendees at specialist drug treatment services [19, 37]. These data should be interpreted with caution: Many countries have expanded efforts to detect and treat cannabis problems; specialist treatment varies greatly and in some countries may extend to harm reduction programs and brief or Internet-delivered interventions; and, in some countries, a significant proportion of referrals to treatment are directed by the educational or criminal justice systems. Only 54% of those entering treatment for cannabis-related problems report using the drug on a daily or nearly daily basis. An additional 10% report using the drug once a week or less, and 15% do not report using it in the month prior to entering treatment. These findings suggest that not all those entering treatment would be diagnosed with CUD.

Oceania The 24 countries of Oceania include Australia, New Zealand, and the estimated 7500 to 10,000 Pacific Island countries and territories (PICT) of Polynesia, Micronesia, and Melanesia. The diverse region is home to around 35 million people, who speak more than 1200 languages and dialects. Australia and New Zealand are highly developed nations, but poverty, political instability, poor governance, and low technical capacity challenge many PICT. Cannabis is produced in Australia, Papua New Guinea, and New Zealand, as well as many of the smaller PICT. Cannabis is illegal across the region but is decriminalized for personal use in some states of Australia. In 2016, medical marijuana became available for certain patients in Australia, and specialist doctors in New Zealand may prescribe nabiximols only for patients who meet strict criteria.

Australia The largest and most populous country, Australia, has systematic, triennial general population surveys of use, experiences, and attitudes toward alcohol, tobacco, and illicit drugs. The Australian Government has conducted the National Drug Strategy Household Survey (NDSHS) every 2–3 years since 1985. In 2016, nearly 24,000 household residents aged 12 years and older responded to a stratified, multistage, random sample design survey. Data analyses focused on people 14 and older to allow comparison with earlier surveys [6, 8]. As in previous surveys, homeless and institutionalized people were not included. Lifetime use of cannabis among Australians aged 14 years and older was stable at 34.8%, down from a high of 39.1% in 1998. One in ten (10.4%) used cannabis in the previous 12 months, and the rates of use have increased since 2013 in all age groups except the youngest (14–19 years). Weekly or more frequent use of cannabis also increased, from 19.5% to 36% in 2016 [7]. The perception of cannabis as a problem drug decreased from 23% to 14%. Use increased significantly among women, who are typically more sensitive to social sanctions against drug use. Indigenous Australians used cannabis at 1.6 times the national rate (16% vs. 10%) [5]. A recent study of cannabis use by Aboriginal women found that 20.5% used cannabis during pregnancy, and, when compared to non-cannabis using mothers, cannabis-using mothers had babies that weighed significantly less and experienced significantly higher rates of negative birth outcomes [11].

The Australian Secondary Students' Alcohol and Drug survey has been conducted since 1984. In 2014, slightly more than 23,000 secondary students aged between 12 and 17 years were asked about their lifetime and current use of tobacco, alcohol, analgesics, tranquilizers, illicit substances, and related behaviors [5]. Cannabis was the most commonly used illicit substance, with lifetime prevalence of 16% and prior month prevalence of 7%. The proportion of students using cannabis increased with age. The most common method of using cannabis was smoking it in a bong; 62% of males and 54% of females who had used cannabis in the past year reported this method of use. There were no significant differences in the proportion of students using cannabis in the past week, past month, or lifetime between 2008 and 2014 or between 2011 and 2014.

The most recent Australian data on the prevalence of CUD is 10 years old and likely underestimates current DSM-5 levels. The prevalence of cannabis abuse was 3.8% for lifetime use and 0.5% for use in the previous 12 months. For CUD, lifetime prevalence was 2.7%, and past-year prevalence was 0.5%. Cannabis dependence was significantly higher in males, younger adults, and those who never married [11]. Australian publicly funded alcohol and other drug treatment service agencies report to a National Minimum Dataset about the number of people they treat and the type of treatment provided. Between 2013–2014 and 2015–2016, an estimated 1 out of 180 people received treatment, an increase of 11% from 118,760 to 133,895 [59]. During the 5 years prior to 2015–2016, four drugs were a factor in 83% of all treatment demands: alcohol (32%), cannabis (23%), amphetamines (23%), and heroin (6%). Cannabis steadily increased as the principal drug of concern, particularly among young people: 66% of patients aged 10–29 years sought treatment for cannabis use. The majority of those receiving treatment for cannabis-related problems were male [59]. Increasing rates of cannabis-related requests for ambulances suggest a growing concern. A 2000 to 2013 study of 15–59-year olds in metropolitan Melbourne found that rates of cannabis-related ambulance attendances increased significantly from 0.6 per 100,000 population per year between 2000 and 2010 to 5.5 per 100,000 population per year between 2010 and 2013 [31].

New Zealand New Zealand is the only other country in Oceania with systematic data on patterns of cannabis use. The 2007–2008 New Zealand Alcohol and Drug Use Survey report on cannabis included patterns of use, drugged driving, harms from use (productivity, learning, and mental health), legal problems, and cutting down and seeking help. The 2012–2013 New Zealand Health Survey (NZHS) assessed cannabis use by 13,000 adults aged 15 years or older. More than 43% of adults reported having used cannabis in their lifetime, and one in ten (11%) reported using cannabis in the last 12 months. Thirty-four percent of cannabis users reported using cannabis at least weekly in the last 12 months. Men (15%) used cannabis more frequently than women (8%) and were more likely to report using cannabis at least weekly in the last 12 months. Among ethnic groups, 25% of Māori reported using cannabis in the last 12 months, compared with 11% of European/Other ethnicity, 9% of Pacific, and 2.9% of Asians. Māori were 2.2 times more likely to report using cannabis in the last 12 months than non-Māori, after adjusting for age and sex differences. Six percent of cannabis users reported harmful effects on work, studies, or employment opportunities: 4.9% reported difficulty learning, and 1.7% reported absence from work or school in the last 12 months due to cannabis use [39].

PICT Little is known about the use of cannabis or other drugs in the PICT due to a lack of reliable, routine data collection and observational systems, particularly among the general population and more vulnerable youth not captured in school surveys. The pattern of cannabis use among PICT adolescents aged 13–17 years attending school is much better understood where countries use the WHO Global Student Health Survey (GSHS) [66] or the US Centers for Disease Control and Prevention Youth Risk Behavior Survey (YRBS) [56]. Rates of cannabis use vary considerably among young

people aged 13–17 years in the Oceania countries for which data are available (Table 26.1); however, results should not be directly compared without great caution. Some variations may be due to the sample size, year, survey instrument, or methodology. The core survey questions remain essentially similar, and survey administrators attempt to ensure that the specific rural versus urban, gender, and ethnic mix of students sampled is representative for the respective countries. Despite these limitations, using comparable survey methods reveals that the Northern Mariana Islands, Palau, Guam, and Samoa occupy four of the top five highest prevalence rates of cannabis use among school students in the world. A 2015 survey of 400 older Solomon Islands adolescents, with a median age of 19 years, found much higher rates of cannabis use: 48% reported ever using cannabis and 33% of 15–19-year-olds reported recent use [40].

Western Hemisphere Drug use in the Western Hemisphere varies widely among countries and regions and within regions. Currently, none of the countries in Latin America and the Caribbean collect systematic data on problem cannabis use, cannabis dependence, or potential need for treatment. In addition to the need for better data on use, reliable information is needed on THC potency; market behavior and supply of cannabis; the impact of cannabis use on health, especially among adolescents and young adults; the determinants of drug use by gender and the associated risks and harms; and patterns of use by gender, social class, and age groups. The Inter-American Drug Abuse Control Commission at the Organization of American States, known by its Spanish-language acronym CICAD, has worked with National Drug Observatories in the region to build capacity for drug abuse epidemiology studies. Most of the data in the region are collected through surveys of secondary school students, with smaller numbers of general population studies or university student surveys [29].

Cannabis is the most common illicit drug used in youth populations across the Western Hemisphere: 21.26% of secondary students report lifetime use. Throughout the region, about 50% of students who reported lifetime use also reported use during the past month. Perception of risk and access to illicit substances correlate with prevalence rates. Only 35% of secondary school students report perceiving risks associated with occasional cannabis use; that figure varies widely. Similarly 32% of secondary school students report that they think it is "easy" to obtain cannabis, with a range between 4.8% in Venezuela and 60.7% in the United States. Direct offers of cannabis are often used to indicate the availability of a drug; 17% of secondary school students reported that they had been offered cannabis in the past year. Just 3.9% of students in the Dominican Republic

Table 26.1 Ever and recent cannabis use among secondary school students in Oceania

Country	Year	Survey	Sample Size	Sex	
				Male	Female
American Samoa	2011	YRBS[a]	2927		
Ever				23.0	7.2
Recent				15.6	3.9
Australia	2014	ASSS[b]	23,007		
Ever				17.1	14.4
Recent				8.3	5.8
Cook Islands	2015	GSHS[c]	1274		
Ever				11.9	8.2
Federated States of Micronesia—Pohnpei	2007	GSHS	280		
Ever				14.5	14.5
Fiji	2016	GSHS	3705		
Ever				10.4	3.3
French Polynesia	2015	GSHS	3216		
Ever				27.0	27.1
Guam	2015	YRBS	1219		
Ever				48.2	50.4
Recent				33.1	26.9
Kiribati	2011	GSHS	1582		
Ever				6.8	1.6
Marshall Islands	2007	YRBS	1323		
Ever				22.4	5.5
Recent				14.1	3.2
New Zealand	2012	NZSSS[d]	8500		
Ever				24.2	22.0
Recent				14.4	11.5
Northern Mariana Islands	2015	YRBS	2355		
Ever				59.4	49.0
Recent				39.5	28.5
Palau	2015	YRBS	519		
Ever				68.5	64.2
Recent				45.8	31.4
Samoa	2011	GSHS	2418		
Ever				43.2	24.7
Solomon Islands	2011	GSHS	1421		
Ever				16.1	11.1
Tokelau	2014	GSHS	140		
Ever				10.4	6.7
Tonga	2010	GSHS	2211		
Ever				4.8	8.0
Tuvalu	2013	GSHS	943		
Ever				11.3	0.0
Vanuatu	2011	GSHS	1119		
Ever				5.0	1.9
Wallis and Futuna	2015	GSHS	1117		
Ever				6.3	2.7
Recent				3.5	1.5

[a]Youth Risk Behavior Survey, US Centers for Disease Control and Prevention [56]
[b]Australian Secondary School Survey, White and Williams [59]
[c]Global School-Based Student Health Survey, World Health Organization [66]
[d]New Zealand Secondary School Survey, Bullen et al. [12]

reported having been offered cannabis in the past year, while 36.5% of students in Antigua and Barbuda reported past-year offers [29].

In Central and South America, regional averages hide the intra-country diversity in past-year prevalence among secondary school students. Although the average of past-year prevalence for South America is 7.21%, Chile reports past-year prevalence of 28.4%; Columbia, 7.08%; and Venezuela, 0.9%. The same pattern is evident in Central American countries: Belize reports 15.84% past-year prevalence, while Honduras reports 1.06%. The Caribbean subregion appears to be the most homogenous in terms of prevalence. Except for Haiti (2.36%) and the Dominican Republic (0.99%), secondary school student past-year cannabis use consistently ranges from above 10% in eight countries to 23.89% in Antigua and Barbuda. Because most of the Caribbean school surveys were carried out in similar time periods between 2011 and 2014, the data are more comparable intra-regionally than in the other subregions [29].

The wide range of lifetime prevalence among secondary school students in South America may imply that higher versus lower prevalence rates may reflect the economic development status of specific countries. Do the relatively high lifetime prevalence rates reported by some countries in the Southern Cone—Argentina (13.9%), Chile (34.89%), and Uruguay (20.10%)—reflect their World Bank classification as upper-middle or high-income countries? In contrast, lifetime prevalence rates are lower among the countries of the Andean subregion—Bolivia (6.2%), Colombia (9.86%), Ecuador (6.7%), and Peru (5.02%)—all classified by the World Bank as lower-middle income economies [29, 62].

As females are increasingly represented in the drug market, many countries have begun to use the term *the feminization of drug use* ([14], p. 27; [55]; and [4], p. 188). Males and females respond differently to drugs due to biological differences, but the risk of violence associated with drug use is increased for women. Secondary school boys use cannabis at higher rates than girls in every country in the Hemisphere; however, the disparities in use between males and females are much lower in high-prevalence countries. In fact, secondary schoolgirls in higher-prevalence countries use cannabis at higher rates than boys in some of the lower-prevalence countries.

Younger and younger people report cannabis use across the Western Hemisphere, beginning in the early years of secondary school. Early initiation of use is a high-risk behavior for adolescents, with the potential for long-term, negative health consequences for the adolescent population and public health in general [60]. Early age of initiation does not correlate with high prevalence rates: while Canada and the United States have some of the highest prevalence rates, more 8th graders use cannabis in seven other nations—Belize, Chile, Dominica, Antigua and Barbuda, Saint Lucia, Saint Vincent and the Grenadines, and Saint Kitts and Nevis. Early use is often a predictive indicator for increasing risk so it may be necessary to look more deeply at other risk factors.

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