DISCUSSION 5

Prior to beginning work on this discussion, read the required chapters from the text and review the required articles for this week.

The risk-benefit calculation for any drug assumes a correct diagnosis of the disorder. Many investigators and clinicians feel the current epidemic of child psychiatric disorders is largely due to inappropriate diagnosis. Evaluate the risk and benefits of using psychoactive drugs in children correctly diagnosed with a disorder versus those incorrectly diagnosed with a disorder. Consider the risks and benefits of not treating (drug treatment) a child because he or she is not correctly diagnosed with a disorder. In your evaluation summarize the natural course of the disorder, the drug action on the neurotransmitter systems in question, and the likelihood of short-term, long-term, and permanent positive and negative effects of drug treatment. Make sure to take into account the ethical dimension of this risk-benefit calculation.

REFERENCE ATTACHED

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

TECHNICAL REPORT

Prenatal Substance Abuse: Short- and Long-term Effects on the Exposed Fetus

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KEY WORDS
prenatal drug exposure, alcohol, nicotine, marijuana, cocaine, methamphetamine, growth and development

ABBREVIATIONS
AAP—American Academy of Pediatrics
THC—tetrahydrocannabinol

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Prenatal substance abuse continues to be a significant problem in this country and poses important health risks for the developing fetus. The primary care pediatrician's role in addressing prenatal substance exposure includes prevention, identification of exposure, recognition of medical issues for the exposed newborn infant, protection of the infant, and follow-up of the exposed infant. This report will provide information for the most common drugs involved in prenatal exposure: nicotine, alcohol, marijuana, opiates, cocaine, and methamphetamine. *Pediatrics* 2013;131:e1009–e1024

Substance abuse has been a worldwide problem at all levels of society since ancient times. Attention has been directed toward the use of legal and illegal substances by pregnant women over the past several decades. Almost all drugs are known to cross the placenta and have some effect on the fetus. The effects on the human fetus of prenatal cigarette use have been identified and studied since the 1960s,[1] the effects of alcohol and opiate use have been studied since the 1970s,[2–4] and the effects a variety of other illicit drugs have been studied since the 1980s.[5–7] This report reviews data regarding the prevalence of exposure and available technologies for identifying exposure as well as current information regarding short- and long-term outcomes of exposed infants, with the aim of facilitating pediatricians in fulfilling their role in the promotion and maintenance of infant and child health.

PREVALENCE

Prevalence estimates for prenatal substance use vary widely and have been difficult to establish. Differences are likely attributable to such things as the use of different sampling methods and drug-detection methods, screening women in different settings, and obtaining data at different points in time. For example, prevalence will vary depending on whether history or testing of biological specimens is used; whether the biological specimen is hair, urine, or meconium; and whether the specimens are merely screened for drugs or screened and confirmed with additional testing. There also will be differences depending on whether the sample being investigated is a community sample or a targeted sample, such as women who are in drug treatment or are incarcerated. Lastly, prevalence must be interpreted in light of the fact

that the use of specific drugs waxes and wanes over time nationwide as the popularity of certain substances changes.

Although a variety of prevalence studies have been conducted over the past 2 decades, there is 1 national survey that regularly provides information on trends in substance abuse among pregnant women. The National Survey on Drug Use and Health (formerly called the National Household Survey on Drug Abuse), sponsored by the Substance Abuse and Mental Health Services Administration (http://www.oas.samhsa.gov/nhsda.htm), is an annual survey providing national and state level information on the use of alcohol, tobacco, and illicit drugs in a sample of more than 67 000 noninstitutionalized people older than 12 years. Data are combined into 2-year epochs and include reported drug use for pregnant women between the ages of 15 and 44 years. Current illegal drug use among pregnant women remained relatively stable from 2007–2008 (5.1%) to 2009–2010 (4.4%). These average prevalence rates are significantly lower than reported current illicit drug use rates for nonpregnant women (10.9%). Importantly, the rate of current drug use among the youngest and possibly the most vulnerable pregnant women was highest (16.2% for 15- to 17-year-olds, compared with 7.4% among 18- to 25-year-olds and 1.9% among 26- to 44-year-olds). Table 1 summarizes these data along with information regarding current alcohol use, binge drinking, and cigarette use by pregnant and nonpregnant women. An additional important finding from this survey was that the rate of cigarette smoking for those 15 to 17 years of age actually was higher for pregnant women than for nonpregnant women (22.7% vs 13.4%, respectively). This report details many sociodemographic variables related to drug use in the American population, and the reader is referred to the Substance Abuse and Mental Health Services Administration Web site for the full report (http://www.oas.samhsa.gov/nhsda.htm).

TABLE 1 Comparison of Drug Use Among Women 15 to 44 Years of Age by Pregnancy Status: 2009–2010

	Pregnant Women, %	Nonpregnant Women, %
Illicit drug use	4.4	10.9
Alcohol use	10.8	54.7
Binge drinking	3.7	24.6
Cigarette use	16.3	26.7

IDENTIFICATION OF PRENATAL EXPOSURE

Two basic methods are used to identify drug users: self-report or biological specimens. Although no single approach can accurately determine the presence or amount of drug used during pregnancy, it is more likely that fetal exposure will be identified if a biological specimen is collected along with a structured interview.[8]

Self-reported history is an inexpensive and practical method for identifying prenatal drug exposure and is the only method available in which information can be obtained regarding the timing of the drug use during pregnancy and the amount used. Unfortunately, self-report suffers from problems with the veracity of the informant and recall accuracy.[9,10] Histories obtained by trusted, nonjudgmental individuals or via computerized survey forms; questions referring back to the previous trimester or prepregnancy usage, not current use; and pregnancy calendars used to assist recollection each improve the accuracy of the information obtained.[11–13]

Several biological specimens can be used to screen for drug exposure. Each specimen has its own individual variations with regard to the window of detection, the specific drug metabolites used for identification, methods of adulteration of the sample, and analytical techniques, thus altering the sensitivity and specificity for each drug of interest. The most common analytical method used for screening biological specimens is an immunoassay designed to screen out drug-free samples. Threshold values generally are set high to minimize false-positive test results but may be too high to detect low-dose or remote exposure. Because immunoassay is a relatively nonspecific test, positive results require confirmation by using gas chromatography/mass spectrometry. In addition, confirmation of the presence of a drug is not always associated with drug abuse. Alternative explanations include passive exposure to the drug, ingestion of other products contaminated with the drug, or use of prescription medications that either contain the drug or are metabolized to the drug.[14] Thus, careful patient histories remain essential to the process of identification.

The 3 most commonly used specimens to establish drug exposure during the prenatal and perinatal period are urine, meconium, and hair; however, none is accepted as a "gold standard." Urine has been the most frequently tested biological specimen because of its ease of collection. Urine testing identifies only recent drug use, because threshold levels of drug metabolites generally can be detected in urine only for several days. A notable exception to this is marijuana, the metabolites of which can be excreted for as long as 10 days in the urine of regular users[15] or up to 30 days in chronic, heavy users. Urine is a good medium as well for the detection of nicotine, opiate, cocaine, and amphetamine exposure.[16,17]

Meconium is also easy to collect noninvasively. It is hypothesized that drugs accumulate in meconium throughout pregnancy, and thus, meconium is

thought to reflect exposure during the second and third trimester of pregnancy when meconium forms. However, use of meconium to determine the timing or extent of exposure during pregnancy is controversial[18] because of a lack of studies regarding the effects of the timing and quantity of the postpartum specimen collection as well as the effects of urine or transitional stool contamination of the meconium samples.[19] Meconium has been used for the detection of nicotine, alcohol, marijuana, opiate, cocaine, and amphetamine exposure.[16,20]

Hair is easy to collect, although some people decline this sampling method because of cosmetic concerns and societal taboos. Drugs become trapped within the hair and, thus, can reflect drug use over a long period of time. Unfortunately, using hair to determine timing and quantity of exposure also is controversial. In addition, environmental contamination, natural hair colors and textures, cosmetic hair processing, and volume of the hair sample available all affect the rational interpretation of the results.[21–24] Hair is useful for the detection of nicotine, opiate, cocaine, and amphetamine exposure.[16,25]

Other biological specimens have been studied for use in the detection of in utero drug exposure but are not commonly used in the clinical setting. These include such specimens as cord blood, human milk, amniotic fluid, and umbilical cord tissue.[8,19,26] In the case of umbilical cord tissue, drug class-specific immunoassays for amphetamines, opiates, cocaine, and cannabinoids appear to be as reliable as meconium testing, with the additional benefit of availability of the tissue at the time of birth.[27]

Beginning in the early 1980s, states began to enact legislation in response to the increasingly popular use of "crack" cocaine in our society. Such laws required the reporting of women who used drugs during pregnancy to the legal system through states' child abuse statutes. In 2003, the Keeping Children and Families Safe Act (Public Law 108-36) was passed by Congress, requiring physicians to notify their state child protective services agency of any infant identified as affected by illegal substances at birth or experiencing drug withdrawal. Currently, issues of whether to use biological specimens to screen for drug abuse; whether to screen the mother, her infant, or both; and which women and infants to screen are issues complicated by legal, ethical, social, and scientific concerns. Each of these concerns must be taken into account as obstetricians, neonatologists, and pediatricians work to develop protocols for identifying prenatal drug exposure. For example, there is no biological specimen that, when obtained randomly, identifies prenatal drug use with 100% accuracy; hence, a negative drug screening result does not ensure that the pregnancy was drug free. Targeted screening of high-risk women is problematic, because it can be biased toward women of racial or ethnic minorities and those who are economically disadvantaged or socially disenfranchised. Universal screening of pregnant women is impractical and not cost-effective.[28–30] Finally, testing of biological specimens when the maternal history is positive for drug use increases medical costs and does not necessarily provide information that guides the medical care of the infant.[31]

MECHANISMS OF ACTION OF DRUGS ON THE FETUS

Drugs can affect the fetus in multiple ways. Early in gestation, during the embryonic stage, drugs can have significant teratogenic effects. However, during the fetal period, after major structural development is complete, drugs have more subtle effects, including abnormal growth and/or maturation, alterations in neurotransmitters and their receptors, and brain organization. These are considered to be the direct effects of drugs. However, drugs also can exert a pharmacologic effect on the mother and, thus, indirectly affect the fetus. For example, nicotine acts on nicotinic cholinergic receptors within the mesolimbic pathway, and neuropathways activated by alcohol enhance inhibitory γ-aminobutyric acid (GABA) receptors and reduce glutamate receptor activity. Drugs of abuse mimic naturally occurring neurotransmitters, such that marijuana acts as anandamides, opiates act as endorphins, and cocaine and stimulants act within the mesolimbic dopaminergic pathways to increase dopamine and serotonin within the synapses.[32] Other indirect effects of drugs of abuse on the fetus include altered delivery of substrate to the fetus for nutritional purposes, either because of placental insufficiency or altered maternal health behaviors attributable to the mother's addiction. These altered behaviors, which include poor nutrition, decreased access/compliance with health care, increased exposure to violence, and increased risk of mental illness and infection, may place the fetus at risk.[33]

Nicotine concentrations are higher in the fetal compartment (placenta, amniotic fluid, fetal serum) compared with maternal serum concentrations.[34–36] Nicotine is only 1 of more than 4000 compounds to which the fetus is exposed through maternal smoking. Of these, ~30 compounds have been associated with adverse health outcomes. Although the exact mechanisms by which nicotine produces adverse fetal effects are unknown, it is likely that hypoxia, undernourishment of

the fetus, and direct vasoconstrictor effects on the placental and umbilical vessels all play a role.[37,38] Nicotine also has been shown to have significant deleterious effects on brain development, including alterations in brain metabolism and neurotransmitter systems and abnormal brain development.[39–43] Additional toxicity from compounds in smoke, such as cyanide and cadmium, contribute to toxicity.[44–48]

Ethanol easily crosses the placenta into the fetus, with a significant concentration of the drug identified in the amniotic fluid as well as in maternal and fetal blood.[49,50] A variety of mechanisms explaining the effects of alcohol on the fetus have been hypothesized. These include direct teratogenic effects during the embryonic and fetal stage of development as well as toxic effects of alcohol on the placenta, altered prostaglandin and protein synthesis, hormonal alterations, nutritional effects, altered neurotransmitter levels in the brain, altered brain morphology and neuronal development, and hypoxia (thought to be attributable to decreased placental blood flow and alterations in vascular tone in the umbilical vessels).[51–69]

Although the main chemical compound in marijuana, δ-9-tetrahydrocannabinol (THC), crosses the placenta rapidly, its major metabolite, 11-nor-9-carboxy-THC, does not.[70] Unlike other drugs, the placenta appears to limit fetal exposure to marijuana, as fetal THC concentrations have been documented to be lower than maternal concentrations in studies of various animal species.[15,70–72] The deleterious effects of marijuana on the fetus are thought to be attributable to complex pharmacologic actions on developing biological systems, altered uterine blood flow, and altered maternal health behaviors.[73–75] Similar to other drugs, marijuana has been shown to alter brain neurotransmitters as well as brain biochemistry, resulting in decreased protein, nucleic acid, and lipid synthesis.[74,76–79] Marijuana can remain in the body for up to 30 days, thus prolonging fetal exposure. In addition, smoking marijuana produces as much as 5 times the amount of carbon monoxide as does cigarette smoking, perhaps altering fetal oxygenation.[80]

In humans, opiates rapidly cross the placenta, with drug equilibration between the mother and the fetus.[81] Opiates have been shown to decrease brain growth and cell development in animals, but studies of their effects on neurotransmitter levels and opioid receptors have produced mixed results.[82–89]

Pharmacologic studies of cocaine in animal models using a variety of species have demonstrated that cocaine easily crosses both the placenta and the blood-brain barrier and can have significant teratogenic effects on the developing fetus, directly and indirectly.[90] Cocaine's teratogenic effects most likely result from interference with the neurotrophic roles of monoaminergic transmitters during brain development,[91–94] which can significantly affect cortical neuronal development and may lead to morphologic abnormalities in several brain structures, including the frontal cingulate cortex.[94] It also appears that the development of areas of the brain that regulate attention and executive functioning are particularly vulnerable to cocaine. Thus, functions such as arousal, attention, and memory may be adversely affected by prenatal cocaine exposure.[89,91,95–97] Furthermore, insults to the nervous system during neurogenesis, before homeostatic regulatory mechanisms are fully developed, differ from those on mature systems. Thus, cocaine exposure occurring during development of the nervous system might be expected to result in permanent changes in brain structure and function, which can produce altered responsiveness to environmental or pharmacologic challenges later in life.[98]

Methamphetamine is a member of a group of sympathomimetic drugs that stimulate the central nervous system. It readily passes through the placenta and the blood-brain barrier and can have significant effects on the fetus.[99–101] After a single dose of methamphetamine to pregnant mice, levels of substance in the fetal brain were found to be similar to those found in human infants after prenatal methamphetamine exposure, with accumulation and distribution of the drug most likely dependent on the monoaminergic transport system. It is possible that the mechanism of action of methamphetamine is an interaction with and alteration of these neurotransmitter systems in the developing fetal brain[100] as well as alterations in brain morphogenesis.[102]

MEDICAL ISSUES IN THE NEWBORN PERIOD

Fetal Growth

Fetal tobacco exposure has been a known risk factor for low birth weight and intrauterine growth restriction for more than 50 years,[103] with decreasing birth weight shown to be related to the number of cigarettes smoked.[104–107] Importantly, by 24 months of age, most studies no longer demonstrate an effect of fetal tobacco exposure on somatic growth parameters of prenatally exposed infants.[108–114] Growth restriction is 1 of the hallmarks of prenatal alcohol exposure and must be present to establish a diagnosis of fetal alcohol syndrome.[3,115] However, even moderate amounts of alcohol use during pregnancy is associated with a decrease in size at birth.[116–119] In general, marijuana has

not been associated with fetal growth restriction, particularly after controlling for other prenatal drug exposures.[109,120-122] Fetal growth effects are reported in studies of prenatal opiate exposure; however, confounding variables known to be associated with poor growth, such as multiple drug use and low socioeconomic status, were not well controlled in many of the studies.[123] Using data from the Maternal Lifestyle Study, Bada et al[124] reported lower birth weight in opiate-exposed newborn infants born at ≥33 weeks' gestation, independent of use of other drugs, prenatal care, or other medical risk factors. An independent effect of prenatal cocaine exposure on intrauterine growth has been the most consistent finding across studies of prenatally exposed infants.[122,125-130] Early studies on prenatal methamphetamine exposure[131] as well as recent studies[132] reveal independent effects of the drug on fetal growth. However, the literature available is limited at this time. Several reviews on the effects of prenatal drug exposure on growth contain additional details.[133–135]

Congenital Anomalies

Nicotine has been associated with oral facial clefts in exposed newborn infants,[136–140] although the data are relatively weak. There is a vast literature on the teratogenic effects of prenatal alcohol exposure after the first description of fetal alcohol syndrome in 1973.[3] The American Academy of Pediatrics (AAP) policy statement "Fetal Alcohol Syndrome and Alcohol-Related Neurodevelopmental Disorders" contains more information.[141] No clear teratogenic effect of marijuana or opiates is documented in exposed newborn infants.[142] Original reports regarding cocaine teratogenicity have not been further documented.[133,143] Studies of fetal methamphetamine exposure in humans are limited. However, Little et al[131] reported no increase in the frequency of major anomalies in a small sample of exposed infants when compared with nonexposed infants.

Withdrawal

No convincing studies are available that document a neonatal withdrawal syndrome for prenatal nicotine exposure. Although several authors describe abnormal newborn behavior of exposed infants immediately after delivery, the findings are more consistent with drug toxicity, which steadily improves over time,[144,145] as opposed to an abstinence syndrome, in which clinical signs would escalate over time as the drug is metabolized and eliminated from the body. There is 1 report of withdrawal from prenatal alcohol exposure in infants with fetal alcohol syndrome born to mothers who drank heavily during pregnancy,[146] but withdrawal symptoms have not been reported in longitudinal studies available in the extant literature. Neonatal abstinence symptoms have not been observed in marijuana-exposed infants, although abnormal newborn behavior has been reported with some similarities to that associated with narcotic exposure.[147] An opiate withdrawal syndrome was first described by Finnegan et al[148] in 1975. Neonatal abstinence syndrome includes a combination of physiologic and neurobehavioral signs that include such things as sweating, irritability, increased muscle tone and activity, feeding problems, diarrhea, and seizures. Infants with neonatal abstinence syndrome often require prolonged hospitalization and treatment with medication. Methadone exposure has been associated with more severe withdrawal than has exposure to heroin.[149] Early reports regarding buprenorphine, a more recent alternative to methadone, suggest minimal to mild withdrawal in exposed neonates. A large multicenter trial evaluating buprenorphine's effect on exposed infants documented decreased morphine dose, hospital length of stay, and length of treatment.[150–152] There has been no substantiation of early reports regarding cocaine withdrawal.[153] Currently, no prospective studies of withdrawal in methamphetamine-exposed infants are available. A retrospective study by Smith et al[154] reported withdrawal symptoms in 49% of their sample of 294 methamphetamine-exposed newborn infants. However, only 4% required pharmacologic intervention. The AAP clinical report on neonatal drug withdrawal contains in-depth information on neonatal drug withdrawal, including treatment options.[155]

Neurobehavior

Abnormalities of newborn neurobehavior, including impaired orientation and autonomic regulation[156] and abnormalities of muscle tone,[144,147,157] have been identified in a number of prenatal nicotine exposure studies. Poor habituation and low levels of arousal along with motor abnormalities have been identified in women who drank alcohol heavily during their pregnancy.[80,158] Prenatal marijuana exposure is associated with increased startles and tremors in the newborn.[120] Abnormal neurobehavior in opiate-exposed newborn infants is related to neonatal abstinence (see earlier section on Withdrawal). Using the Brazelton Newborn Behavioral Assessment Scale,[159] reported effects of prenatal cocaine exposure on infants have included irritability and lability of state, decreased behavioral and autonomic regulation, and poor alertness and orientation.[160] Recent data from the Infant Development, Environment, and Lifestyle multicenter study on the effects of prenatal methamphetamine exposure documented abnormal

neurobehavioral patterns in exposed newborn infants consisting of poor movement quality, decreased arousal, and increased stress.[161]

Breastfeeding

Few sources are available documenting the prevalence of drug use during breastfeeding. Lacking recent data, the 1988 National Maternal and Infant Health Survey (http://www.cdc.gov/nchs/about/major/nmihs/abnmihs.htm) revealed that the prevalence of drug use during pregnancy was comparable to the prevalence of use among women who breastfed their infants. Women who used various amounts of alcohol or marijuana and moderate amounts of cocaine during their pregnancy were not deterred from breastfeeding their infants. Thus, the pediatrician is faced with weighing the risks of exposing an infant to drugs during breastfeeding against the many known benefits of breastfeeding.[162] For women who are abstinent at the time of delivery or who are participating in a supervised treatment program and choose to breastfeed, close postpartum follow-up of the mother and infant are essential.

For most street drugs, including marijuana, opiates, cocaine, and methamphetamine, the risks to the infant of ongoing, active use by the mother outweigh the benefits of breastfeeding, because most street drugs have been shown to have some effect on the breastfeeding infant.[163–166] In addition, the dose of drug being used and the contaminants within the drug are unknown for most street drugs. Nicotine is secreted into human milk[167,168] and has been associated with decreased milk production, decreased weight gain of the infant, and exposure of the infant to environmental tobacco smoke.[169–171] Alcohol is concentrated in human milk. Heavy alcohol use has been shown to be associated with decreased milk supply and neurobehavioral effects on the infant.[172–174] However, for nicotine and alcohol, the benefits of breastfeeding in the face of limited use of these drugs outweigh the potential risks. Marijuana has an affinity for lipids and accumulates in human milk,[175] as can cocaine[26] and amphetamines.[101,165] Although the AAP considers the use of marijuana, opiates, cocaine, and methamphetamine to be a contraindication to breastfeeding, supervised methadone use not only is considered to be compatible with breastfeeding, with no effect on the infant or on lactation, but also is a potential benefit in reducing the symptoms associated with neonatal abstinence syndrome. Several available reviews provide more detailed information with regard to breastfeeding and substance abuse.[162,176] The reader is also referred to the AAP policy statement "Breastfeeding and the Use of Human Milk."[177]

LONG-TERM EFFECTS RELATED TO PRENATAL DRUG EXPOSURE

Growth

The effects of prenatal tobacco exposure on long-term growth are not clear-cut. Reports in the literature of effects on height and weight[178–181] have not been substantiated by research teams able to control for other drug use in the sample.[109,117,182,183] Recent studies, some of which include adolescents, have suggested that the effect on growth might be attributable to a disproportionate weight for height, such that prenatally exposed children were more likely to be obese as evidenced by a higher BMI, increased Ponderal index, and increased skinfold thickness.[113,183,184] A robust and extensive literature is available documenting the effects of prenatal alcohol exposure on long-term growth. Although poor growth is 1 of the hallmarks of fetal alcohol syndrome, it is the least sensitive of the diagnostic criteria.[185] No independent effect of prenatal marijuana exposure on growth has been documented throughout early childhood and adolescence.[109,182,184] Long-term effects on growth have not been documented in the opiate-exposed child.[186] The available literature on the effect of prenatal cocaine exposure on growth throughout childhood is not conclusive. Although several studies document the negative effects of prenatal cocaine exposure on postnatal growth,[187–189] others do not.[126,190,191] No studies are available linking prenatal methamphetamine exposure to postnatal growth problems. However, 1 study of unspecified amphetamine use suggests that in utero exposure may be associated with poor growth throughout early childhood.[192]

Behavior

After controlling for a variety of potentially confounding socioeconomic, psychosocial, family, and health variables, a number of studies have identified independent effects of prenatal tobacco exposure on long-term behavioral outcomes extending from early childhood into adulthood. For example, impulsivity and attention problems have been identified in children prenatally exposed to nicotine.[193–195] In addition, prenatal tobacco exposure has been associated with hyperactivity[196] and negative[197] and externalizing behaviors in children,[198–200] which appear to continue through adolescence and into adulthood in the form of higher rates of delinquency, criminal behavior, and substance abuse.[201–206] Prenatal alcohol exposure is linked with significant attention problems in offspring[207–210] as well as adaptive behavior problems spanning early childhood to adulthood.[211] Problems identified included disrupted school experiences, delinquent

and criminal behavior, and substance abuse. Kelly et al[212] published an in-depth review of the effects of prenatal alcohol exposure on social behavior. Inattention and impulsivity at 10 years of age have been associated with prenatal marijuana exposure.[213] Hyperactivity and short attention span have been noted in toddlers prenatally exposed to opiates,[214] and older exposed children have demonstrated memory and perceptual problems.[215] Caregiver reports of child behavior problems in preschool-aged[216] and elementary school-aged children[217,218] have not been related to cocaine exposure, except in combination with other risk factors.[219–221] However, in longitudinal modeling of caregiver reports at 3, 5, and 7 years of age, the multisite Maternal Lifestyles Study revealed that prenatal cocaine exposure had an independent negative effect on trajectories of behavior problems.[222] There have been teacher reports of behavior problems in prenatally exposed children,[223] although again, findings have not been consistent across studies,[190] and some have been moderated by other risks.[224] There also have been reports in this age group of deficits in attention processing[190] and an increase in symptoms of attention-deficit/hyperactivity disorder and oppositional defiant disorder self-reported by the exposed children.[217,218] To date, no studies are available that link prenatal methamphetamine exposure with long-term behavioral problems. However, 1 study of unspecified amphetamine use during pregnancy suggests a possible association with externalizing behaviors and peer problems.[225,226]

Cognition/Executive Functioning

The link between prenatal nicotine exposure and impaired cognition is not nearly as strong as the link with behavioral problems. However, studies of both young and older children prenatally exposed to nicotine have revealed abnormalities in learning and memory[227,228] and slightly lower IQ scores.[201,229–231] Prenatal alcohol exposure frequently is cited as the most common, preventable cause of nongenetic intellectual disability. Although IQ scores are lower in alcohol-exposed offspring,[207,232] they can be variable. Additionally, prenatal alcohol exposure has been associated with poorer memory and executive functioning skills.[233] Marijuana has not been shown to affect general IQ, but it has been associated with deficits in problem-solving skills that require sustained attention and visual memory, analysis, and integration[230,231,234–236] and with subtle deficits in learning and memory.[237] Longitudinal studies of prenatal opiate exposure have not produced consistent findings with regard to developmental sequelae. Although developmental scores tend to be lower in exposed infants, these differences no longer exist when appropriate medical and environmental controls are included in the analyses.[238–240] With little exception,[241] prenatal cocaine exposure has not predicted overall development, IQ, or school readiness among toddlers, elementary school-aged children, or middle school-aged children.[190,242–250] However, several studies have revealed alterations in various aspects of executive functioning,[221,241] including visual-motor ability,[244] attention,[251–253] and working memory.[254] To date, limited data are available revealing an association between prenatal methamphetamine exposure and IQ.[255]

Language

Poor language development in early childhood after prenatal nicotine exposure has been reported,[227,256,257] as have poor language and reading abilities in 9- to 12-year-olds.[258] Prenatal alcohol exposure has been shown to interfere with the development and use of language,[259] possibly leading to long-term problems in social interaction.[260] No effect of prenatal marijuana exposure on language development has been identified in children through 12 years of age.[227,258] Subtle language delays have been associated with prenatal cocaine exposure.[256,261,262] Currently, no data are available relating the prenatal use of opiates or methamphetamine to language development in exposed offspring.

Achievement

The literature available evaluating academic achievement is limited. In nicotine-exposed children, Batstra et al[200] identified poorer performance on arithmetic and spelling tasks that were part of standardized Dutch achievement tests. Howell et al[232] reported poorer performance in mathematics on achievement tests in adolescents who had been exposed prenatally to alcohol. Streissguth et al[263] describe a variety of significant academic and school problems related to prenatal alcohol exposure, primarily associated with deficits in reading and math skills throughout the school years.[263–266] Prenatal marijuana exposure has been associated with academic underachievement, particularly in the areas of reading and spelling.[267] School achievement is not an area that has been studied adequately with regard to prenatal opiate exposure. Reported effects of cocaine exposure on school achievement are variable. In the longitudinal Maternal Lifestyle Study, 7-year-old children with prenatal cocaine exposure had a 79% increased odds of having an individualized educational plan (adjusted for IQ),[268] and Morrow et al[249] found 2.8 times the risk of learning disabilities among children with prenatal cocaine exposure

compared with their peers who were not exposed to drugs prenatally. However, other studies do not support significant cocaine effects on school achievement.[190,269] No data are available for the effects of methamphetamine on school achievement. Cernerud et al[270] reported on 65 children prenatally exposed to amphetamines. At 14 to 15 years of age, the children in their cohort scored significantly lower on mathematics tests than did their classmates who were not exposed to amphetamines prenatally and had a higher rate of grade retention than the Swedish norm.

Predisposed to Own Drug Use

A limited number of studies are available that have investigated the association between prenatal substance exposure and subsequent drug abuse in exposed offspring. These studies did not document cause and effect, and it remains to be determined how much of the association can be linked to prenatal exposure versus socioeconomic, environmental, and genetic influences. Studies available for prenatal nicotine exposure suggest an increased risk of early experimentation[271] and abuse of nicotine in exposed offspring.[272,273] Brennan et al[274] reported an association of prenatal nicotine exposure with higher rates of hospitalization for substance abuse in adult offspring. Mounting clinical data support an increased risk of ethanol abuse later in life after prenatal exposure.[275,277] Prenatal marijuana exposure has been associated with an increased risk for marijuana and cigarette use in exposed offspring.[273] Insufficient data are available to draw any conclusions relative to the affects of prenatal opiate, cocaine, or methamphetamine exposure on the risk for tobacco, problem alcohol, or illicit drug use later in life.

SUMMARY

Although methodologic differences between studies and limited data in the extant literature make generalization of the results for several of the drugs difficult, some summary statements can be made by using the current knowledge base (Table 2).

The negative effect of prenatal nicotine exposure on fetal growth has been known for decades; however, longitudinal studies do not reveal a consistent effect on long-term growth. Clinical studies have failed to reach a consensus regarding congenital anomalies, and there is no evidence of a withdrawal syndrome in the newborn infant. Recent studies document a negative effect of prenatal exposure on infant neurobehavior as well as on long-term behavior, cognition, language, and achievement.

Alcohol remains the most widely studied prenatal drug of abuse, and the evidence is strong for fetal growth problems, congenital anomalies, and abnormal infant neurobehavior. There has been no convincing evidence of a neonatal withdrawal syndrome. Ongoing longitudinal studies continue to document long-term effects on growth, behavior, cognition, language, and achievement, and alcohol is the most common identifiable teratogen associated with intellectual disability.

Although there have been studies revealing subtle abnormalities in infant neurobehavior related to prenatal marijuana exposure, there have been no significant effects documented for fetal growth, congenital anomalies, or withdrawal. Long-term studies reveal effects of prenatal exposure on behavior, cognition, and achievement but not on language or growth.

The most significant effect of prenatal opiate exposure is neonatal abstinence syndrome. There have been documented effects on fetal growth (but not on long-term growth) and infant neurobehavior as well as long-term effects on behavior. There is not a consensus as to the effects of prenatal opiate exposure on cognition, and few data are available regarding language and achievement.

TABLE 2 Summary of Effects of Prenatal Drug Exposure

	Nicotine	Alcohol	Marijuana	Opiates	Cocaine	Methamphetamine
Short-term effects/birth outcome						
Fetal growth	Effect	Strong effect	No effect	Effect	Effect	Effect
Anomalies	No consensus on effect	Strong effect	No effect	No effect	No effect	No effect
Withdrawal	No effect	No effect	No effect	Strong effect	No effect	*
Neurobehavior	Effect	Effect	Effect	Effect	Effect	Effect
Long-term effects						
Growth	No consensus on effect	Strong effect	No effect	No effect	No consensus on effect	*
Behavior	Effect	Strong effect	Effect	Effect	Effect	*
Cognition	Effect	Strong effect	Effect	No consensus on effect	Effect	*
Language	Effect	Effect	No effect	*	Effect	*
Achievement	Effect	Strong effect	Effect	*	No consensus on effect	*

* Limited or no data available.

Prenatal cocaine exposure has a negative effect on fetal growth and subtle effects on infant neurobehavior. However, there is little evidence to support an association with congenital anomalies or withdrawal. There is not a consensus regarding the effects of prenatal cocaine exposure on either long-term growth or achievement; however, there are documented long-term effects on behavior and subtle effects on language. Although there is little evidence to support an effect on overall cognition, a number of studies have documented effects on specific areas of executive function.

Studies on prenatal methamphetamine exposure are still in their infancy. Early studies have documented an effect of prenatal exposure on fetal growth and infant neurobehavior but no association with congenital anomalies and no data regarding infant withdrawal or any long-term effects.

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Psychoactive Drug that is of interest to me is Cannabis:

Assignment 5

Select a psychoactive drug that is of pharmacological interest to you, but not one you will review as part of your Critical Review or one that was included in your previous Rapid Reviews. For this paper, you may choose drugs of abuse; however, the paper must focus on the pharmacology of the drug and not on the social or addictive aspects. If you focus on addiction and social impact, your paper will not receive credit.

In addition to the text, research a minimum of three peer-reviewed articles published within the last five years on your selected drug. Prepare a three-page summary of the drug using the PSY630 Rapid Review Example paper (Links to an external site.) as a guide.
In your Rapid Review, analyze and explain the pharmacological aspects of the drug as they relate to the following: neurotransmitters affected, receptors, route of administration, half-life, doses, side effects, drug interactions, contraindications, and other important facets of the drug. Explain these aspects of the drug in terms of the psychiatric disorders indicated for the drug and the issue(s) associated with that use. If there is no accepted therapeutic use for the drug, evaluate and describe the actions of the drug with regard to the abuse process.

The paper:

- Must be three to five double-spaced pages in length, excluding title page and references page, and it must be formatted according to APA style as outlined in the Ashford Writing Center. (Links to an external site.)
- Must include a title page with the following:
  - Title of paper
  - Your name
  - Course name and number
  - Your instructor's name
  - Date submitted
- Must address the topic of the paper with critical thought.
- Must use at least three peer-reviewed sources in addition to the text.
- Must document all sources in APA style as outlined in the Ashford Writing Center.
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CHAPTER 9

Cannabis: A New Look at an Ancient Plant

Although the hemp plant, *cannabis*, commonly called *marijuana*, has an ancient history of medical, utilitarian, and recreational use, we have only recently begun to understand how it acts in the brain to produce its effects. Cannabis—or, more specifically, its main psychoactive ingredient, *tetrahydrocannabinol* (THC)—is unique because it has stimulatory, sedating, analgesic, and hallucinatory effects, yet is not chemically related to the classical psychostimulants, sedative/hypnotics, analgesics, or hallucinogens. Moreover, during the past few years, social, legal, and economic changes have created several additional challenges in efforts to study this drug. First, advances in cultivation have produced much more varied and potent strains of the plant than in the past. This has made the older literature less relevant to the effects of current use. Second, changes in social attitudes and legal status at the state level have exposed a greater number of people, especially young people, to cannabis than ever before. At the same time, at the national level, cannabis is still placed in the most restrictive legal category, making scientific study more difficult. Third, synthetic cannabinoid use has become much more common and dangerous because of dozens of new formulations, collectively known as spice (or herbal incense).

Spice is dried, shredded plant material treated with a synthetic cannabinoid analog (an *analog* is one of a group of chemical compounds that are similar in structure and pharmacology). These novel compounds are designed to avoid legal penalties and the speed with which they appear on the street makes it very difficult to characterize their toxic effects. For example, by February 2015, more than 250 new substances appeared in the place of the first synthetic cannabinoids to be banned by the Drug Enforcement Administration in 2011 (Fattore, 2016). Finally, the increased acceptance of cannabis for medical applications has rejuvenated pharmacological research into its therapeutic possibilities (Kendall and Yudowski, 2016). In particular, one of the many ingredients in cannabis, *cannabidiol* (CBD), has continued to show medicinal promise. CBD is devoid of psychoactive properties, but appears to have potential for wide medical use, possibly including treatments for

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a variety of sources and at different points in time. Although large-scale surveys provide the best available evidence, they are understood to be only best-guess estimates. According to data from 596,500 adults, who participated in the annual U.S. National Survey on Drug Use and Health from 2002 to 2014, the number of adults who said they used marijuana in the previous year increased from 10.4 percent of respondents to 13.3 percent. Meanwhile, the proportion of adults who perceived great risk of harm from smoking marijuana once or twice a week dropped from 50.4 percent to 33.3 percent. Overall, it was estimated that the number of U.S. adults who use marijuana grew from 21.9 million in 2002 to 31.9 million in 2014. In 2002, 823,000 adults used marijuana for the first time in the past year; in 2014, that number grew to 1.4 million. The number of daily or near-daily users was 8.4 million in 2014, compared with 3.9 million in 2002 (Compton et al., 2016). Evidently, the increased use of cannabis is accompanied by a perceived decrease in risk.

In adolescents, from 1996 to 2016, past-month marijuana use was mostly steady among 8th, 10th, and 12th graders. In 2016, that value for 12th grade was 22.5 percent; for 10th grade, 14.0 percent; and for 8th grade, 5.4 percent. Although 68.9 percent of high school seniors do not view regular marijuana smoking as harmful, 68.5 percent say they disapprove of regular marijuana smoking. In contrast, annual prevalence of synthetic marijuana, such as "spice" and "K2," in 2015, was down for the three grades, reflecting a considerable drop in use; in college students, past-year use of synthetic marijuana fell 80 percent between 2011 and 2015 (Johnston et al., 2016; National Institute on Drug Abuse, 2016).

HISTORY

Cannabis may be the oldest cultivated plant not used for food; the earliest known evidence of cannabis use consists of fibers found in China that date to about 4000 BCE. The ancient cultures of China, India, and Tibet treated numerous ailments with the plant, including gastrointestinal illness, seizures, malaria, pain of childbirth, and snakebite. Various religious groups, such as Buddhists and Hindus, incorporated cannabis into their religious ceremonies, and recreational use was also widespread. Gradually, cannabis use spread to Asia and the Middle East. The plant had many applications and its primary behavioral effects were well known; it was used for fiber (to make rope and cloth), oil, and medicine, as well as for intoxication. For example, the ancient Greek physician Galen cautioned that its use might lead to "senseless talk." During the Middle Ages, it came to the Muslim world and Africa, where its use did not fall under the Muslim prohibition of alcohol. Over centuries,

cannabis was said to have many, sometimes contradictory, properties. It could make you crave sweets, get "high," improve sex and creativity, and also decrease the sex drive, produce insanity, and cause an "amotivational" syndrome. The word *assassin* is thought to derive from the word *hashishiyya*, believed to describe common criminals who also used hashish.

Spaniards brought cannabis to America in 1545, where it was cultivated to manufacture rope for naval use—crucial for overseas empires dependent on sailing ships. For this reason, and since cannabis did not grow well in England, Sir Walter Raleigh was ordered to cultivate hemp in Virginia in 1611 alongside another important cash crop: tobacco. From that time onward, hemp became a staple crop of the American colonists for making rope, clothes, and paper. Even George Washington grew hemp on his plantation. Before the cotton gin was introduced at the end of the eighteenth century, hemp was grown on more acreage than cotton.

After Napoleon's army brought cannabis back from Egypt in the early nineteenth century, its use for both medical and recreational purposes began to spread in the West. In the United States, drug companies marketed cannabis tinctures for medicinal use until the Pure Food and Drug Act of 1906 and the Harrison Narcotic Act of 1914 began to impose constraints. Not specifically outlawed, recreational cannabis use increased in the United States when the Eighteenth Amendment of 1920 prohibited alcohol consumption, facilitated in part by migrant workers coming from Mexico to the United States. In 1930, Harry Anslinger, the first commissioner of the Federal Narcotics Bureau, tried to eradicate cannabis. In the wake of the repeal of the Eighteenth Amendment and the end of Prohibition in 1933, he devised dramatic media attacks that led to the Marijuana Tax Act of 1937. This law did not directly outlaw cannabis, but imposed a tax on it, and it effectively ended legal medicinal use of cannabis until 1969, when the Supreme Court declared the law illegal because imposing a tax on someone who wants to possess an illegal substance is a form of self-incrimination. In 1970, the Comprehensive Drug Abuse Prevention and Control Act (also called the "Controlled Substances Act") reduced the federal penalty for possession from a felony to a misdemeanor.

In November 1996, California passed Proposition 215, the Compassionate Use Act, into law, which allowed patients with a valid physician's prescription to possess and cultivate marijuana in the state for medical use in the treatment of severe conditions, including cancer, acquired immunodeficiency syndrome (AIDS), chronic pain, and spasticity. As of December 2016, 28 states and the District of Columbia have laws legalizing marijuana for medicinal purposes. Currently, seven of these

states and the District of Columbia have also adopted laws legalizing marijuana for recreational use; three of these states—California, Massachusetts, and Nevada—passed measures in November 2016 (for details and updates, see Governing.com, 2016; ProCon.org, 2017, Kilmer, 2017).

Recently, the governors of Rhode Island and Washington and a New Mexico resident, Bryan A. Krumm, petitioned the Drug Enforcement Administration (DEA) to remove marijuana from Schedule I classification. The agency had previously rejected a similar request in 2011, touching off a legal battle to force reclassification in which the DEA ultimately prevailed. In August 2016, the DEA again denied the petition to reclassify cannabis, ruling "there is no substantial evidence that marijuana should be removed from Schedule I" of the Controlled Substances Act. The DEA said in a letter that the drug has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and lacks accepted safety for use under medical supervision.

The DEA, however, also announced a relaxation of its policy on growing cannabis for federally approved research. According to the *Washington Post* (Bernstein, 2016), scientists in academic institutions argue that the regulations imposed on research of Schedule I drugs make it harder to assess whether they may be useful. The new policy, designed to foster research, expands the number of manufacturers that can register with the DEA, although the exact number is not known. Nevertheless, it is thought that the National Institute on Drug Abuse (NIDA) and the University of Mississippi will lose their exclusive control of cannabis cultivation, increasing the amount and diversity of the compounds for investigation. At that point, the DEA, rather than NIDA, would be responsible for allowing the plant to be grown. In September 2017, Senator Orrin Hatch (R-UT) proposed a bill, The Marijuana Effective Drug Study Act of 2017, which would "streamline" the procedure for registering and increase the quota of marijuana allowed for medical and scientific research.

The current inconsistent legal status of cannabis has produced some problems in the cultural response to this drug. Even in those states in which it is medically allowed, the accuracy of the dose and label of these products is poor. Vandrey and colleagues (2015) found that of 75 products purchased (47 different brands), only 17 percent accurately labeled the amount of THC content they contained; 23 percent contained more THC than labeled; and 60 percent contained less THC than labeled. Two commercially available e-cigarette liquid formulations reported to contain 3.3 mg/mL of the cannabis component, cannabidiol, as the active ingredient, instead

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At the same time, the ongoing epidemic of opiate use (see Chapter 10) has put pressure on the medical establishment to limit prescriptions for those analgesics. With increasing constraints on opiates and a more liberal approach to cannabis, it is not surprising that the latter drug may be viewed as a substitute and that patients may seek guidance on this issue from practitioners (Choo et al., 2016). In fact, it is already the case that marijuana is being used in place of FDA-approved drugs in states that have legalized marijuana's medical use, according to a Health Affairs study. Prescription-drug use in conditions thought to benefit from marijuana use (for example, anxiety, pain, and sleep disorders) has dropped in states that legalized medical marijuana, compared to states without legalization (Bradford and Bradford, 2016). The use of drugs not associated with a marijuana benefit, such as antibiotics and anticoagulants, did not differ between the groups of states. It was

estimated that Medicare spending, both by the program and by its beneficiaries, fell by some $165 million in 2013 as the result of marijuana substitution. It has been noted that clinicians have been put in an untenable position of being asked to prescribe a drug that is a controlled substance with undocumented benefits and known harms (D'Souza and Ranganathan, 2015). As argued by Richter and Levy (2014), it may be time to devise governmental regulatory policy in preparation for eventual legalization. Towards that goal, Thomas and Pollard (2016) discuss aspects of a regulatory system that need to be put in place to ensure standardization for the researcher and to reduce the hazards of contamination and inaccurate dosage. Kilmer (2017) provides a thoughtful analysis of the public health and legal consequences that need to be considered as a result of cannabis legalization.

WHAT IS CANNABIS?

The plant genus for cannabis includes three accepted species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabis sativa grows throughout the world and flourishes in most temperate and tropical regions. There are at least 400 different compounds in the plant, of which more than 60 are psychoactive. In 1964, Gaoni and Mechoulam first identified the primary active ingredient, delta-9-tetrahydrocannabinol (THC) (Figure 9.1A), which renewed interest in the field and led to the discovery of the endogenous endocannabinoids (Figure 9.1B).

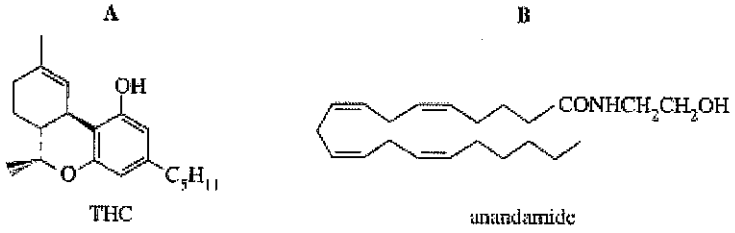

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FIGURE 9.1 Structures of delta-9-tetrahydrocannabinol (THC) and anandamide, the endogenous ligand (neurotransmitter) of the cannabinoid receptor.

The components of the cannabis plant include marijuana, hashish, charas, bhang, ganja, and sinsemilla. Hashish and charas, which consist of the dried resinous exudates of the female flowers, are the most potent preparations; ganja and sinsemilla refer to the dried material found in the tops of the female plants, where the THC content is less. Bhang and marijuana are preparations taken from the dried remainder of the plant, and their THC content is the lowest. However,

with advances in cultivation techniques, the concentration of THC in marijuana has increased from about 3 percent in the 1980s to about 12 percent in 2014 (ElSohly et al., 2016). Among the other cannabis constituents with biologic activity, one, cannabidiol, has attracted recent attention in the medical community. Unlike THC, CBD does not produce a psychedelic effect. In general, as shown in Figure 9.2, as strains of cannabis increase in THC concentration, amounts of CBD decrease. The reverse is also true: as levels of CBD increase, THC amounts tend to decrease. Therefore, certain strains are more potent as psychedelics, while other strains have little psychedelic action and perhaps more therapeutic potential.

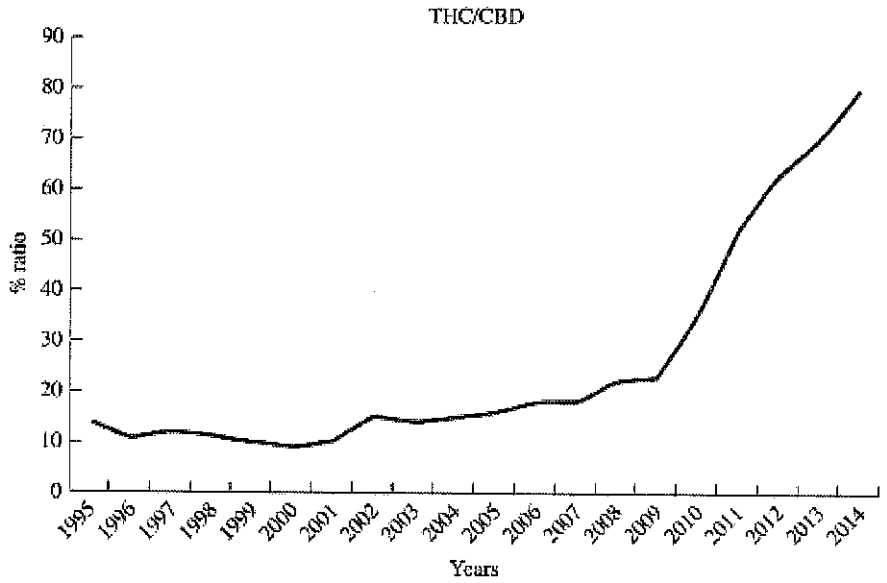

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FIGURE 9.2 The THC-to-CBD ratio over time. During the period 1995 to 2014, as strains of cannabis increased in THC concentration, the amounts of CBD decreased.

[Data from ElSohly et al., 2016.]

Forms of THC and CBD in Cannabis

THC and CBD do not naturally occur in cannabis. Instead, they occur as acidic forms called *tetrahydrocannabinolic acid* (THCa) and *cannabidiolic acid* (CBDa). When burned in a cigarette or heated in cooking or extraction, THCa and CBDa are converted to their active forms, THC and CBD, in a reaction called *decarboxylation*. Perhaps this is why merely chewing the marijuana leaves does not result in a psychedelic effect, in contrast to chewing raw coca leaves. Of note, drying

these brain structures (Figure 9.3). Because there are relatively few cannabis receptors in the brain stem, THC and other agonists have very low toxicity, except at extremely high concentrations. CB2 receptors are mostly (but not completely) found outside the CNS, primarily in tissues of the immune system, such as the tonsils and thymus. In inflammatory conditions, however, CB2 receptors can be found on the microglia cells that are activated to protect the brain.

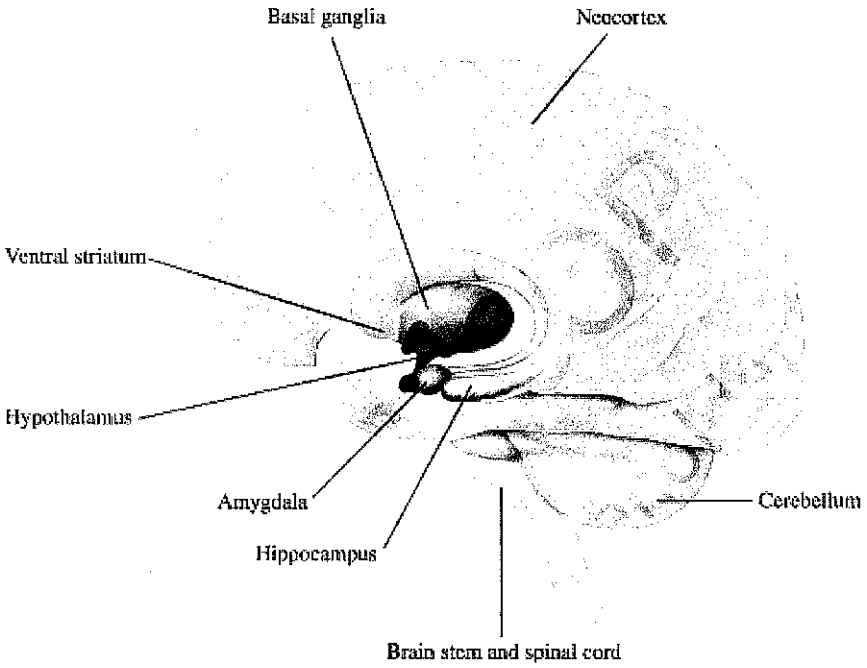

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FIGURE 9.3 Cannabis produces its psychoactive effects by binding to receptors in several brain sites. These receptors are most concentrated in brain structures that regulate higher-order functions, such as judgment (neocortex), learning and memory (the hippocampus), anxiety (amygdala), drug "high" (ventral striatum), movement (basal ganglia and cerebellum), ingestion (hypothalamus), pain, and the vomiting reflex (brain stem and spinal cord).

Dopaminergic neurons are responsible for many of the positive subjective effects of THC. But the relationship between cannabinoid and dopamine systems is so complicated that it has produced conflicting evidence from research in humans and animals. Dopaminergic activity is increased by short-term THC use, while chronic use reduces such effects, although the details of long-term use are not yet clear (Bloomfield et al., 2016).

One reason it has been difficult to specify the precise effects of cannabis may be due to a phenomenon known as "functional selectivity" or "biased agonism." It has

not only depend on targeting a specific G protein–coupled receptor, but also on the particular pathway, inside the cell, that this receptor activates.

Receptor Actions of THC and CBD

Mechanistically, how do THC and CBD differ in their receptor actions? First, THC is a *partial agonist* at CB1 and CB2 receptors. In contrast, CBD does not directly stimulate either receptor, although it may have indirect actions as a *partial antagonist* at CB1 receptors. It therefore can antagonize certain actions of THC. For example, THC can precipitate psychotic reactions, whereas CBD may block this action and may therefore be useful in treating THC-induced psychosis as well as schizophrenia (discussed later in the chapter). In higher doses, CBD functions as a serotonin-1A agonist. CBD also modulates a variety of other receptors in the CNS, such as a receptor that transmits pain sensations. In addition, CBD appears to affect the endogenous cannabinoids (see the next section): it inhibits the breakdown of one endocannabinoid, anandamide, prolonging the effect of this neurotransmitter. Furthermore, it appears to stimulate the release of another endogenous cannabinoid, 2-AG.

ENDOCANNABINOIDS

The discovery of the receptors through which THC produces its effects had significant implications. According to Dr. Raphael Mechoulam (2010):

> So now we are sure of two receptors that are present, and THC acts on them and stimulates them. . . . Now receptors are not present in the body because there is a plant outside there. They are present in the body in order to be activated by something the body produces when and where needed. So we went ahead looking for the compounds in the brain and periphery that would activate these receptors. And in 1992 and 1995, we reported the most important ones. One of them we called anandamide. Ananda comes from the Sanskrit name supreme joy, we were happy after working so hard identifying the compound. Which has, it turns out, to have a different chemical structure from the compound in the plant. It

was rather strange, I would say, because the two compounds do exactly the same.

In Dr. Mechoulam's laboratory, Devane and coworkers (1992) isolated the first endogenous cannabinoid (eCB), anandamide, also known as *N*-arachidonoyl-ethanolamine (AEA) (see Figure 9.1B). Its pharmacology is similar to THC, although its chemical structure is different. Anandamide binds to the central (CB1) and, to a lesser extent, peripheral (CB2) cannabinoid receptors. It is found in nearly all tissues in a wide range of animals. AEA is a partial agonist at CB1 receptors and a partial agonist, or antagonist, at CB2 receptors (Seely et al., 2011).

Soon after the discovery of AEA, a second endogenous cannabinoid (eCB) was found, 2-arachidonoyl glycerol (2-AG). 2-AG binds as a full agonist to both CB1 and CB2 receptors. It is found in even higher concentration in the brain than AEA. Since then, five more substances have been reported to function as endogenous, biologically active cannabinoid substances. Their names and chemical structures are shown in Figure 9.4.

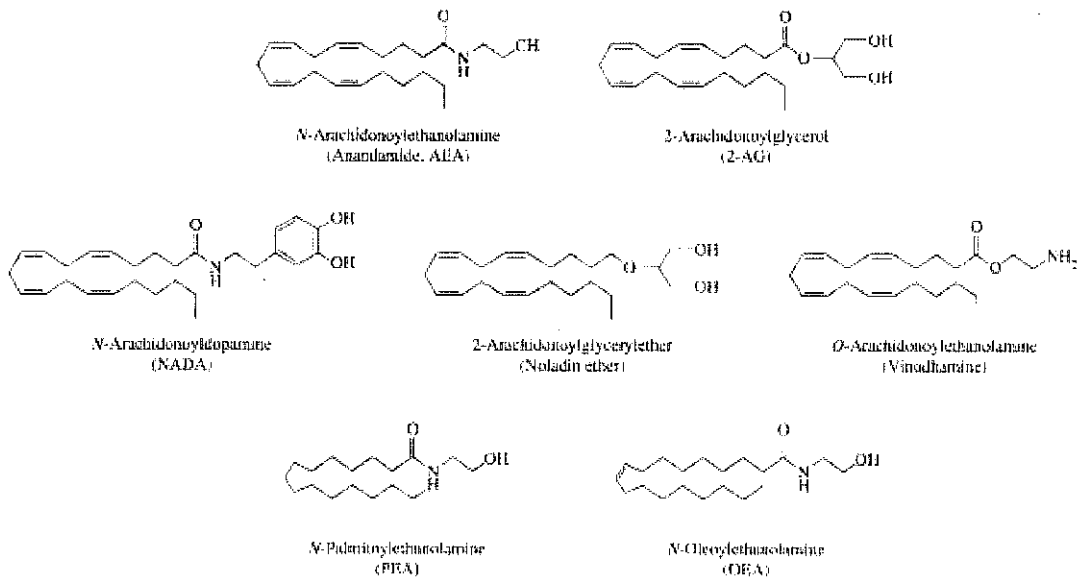

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FIGURE 9.4 Chemical structures of the biologically active endogenous cannabinoid compounds.

As endogenous neurotransmitters, the eCBs are produced, released, removed, and inactivated by processes similar to those of other neurotransmitters. There are important differences, however. First, unlike typical neurotransmitters, AEA and 2-AG are not produced ahead of time and stored in the vesicles of neuronal terminals. Rather, they are synthesized on demand. What this means is that only after a

postsynaptic endocannabinoid neuron is stimulated (for example, by transmitter released from a presynaptic neuron) does it begin to produce AEA or 2-AG. The transmitter opens calcium channels in the postsynaptic eCB neuron. Calcium entry activates specific enzymes, which then produce either AEA or 2-AG. Once these compounds are synthesized, they immediately diffuse out of the neuron into the synaptic space because they are very lipid soluble.

The second way this system differs from a classical transmitter function is that once the eCBs are produced and diffuse out of the postsynaptic neuron, they move back to the presynaptic neuronal terminal, where they bind to CB receptors. That is, eCBs move in a *retrograde* direction and attach to receptors on the presynaptic neuron. By binding to presynaptic CB receptors, they ultimately inhibit further release of transmitter from the presynaptic terminal. In summary, eCBs are released from depolarized postsynaptic neurons and then travel back to presynaptic neurons, where they activate CB receptors to further reduce transmitter release, such as GABA or glutamate. This represents an important way of modulating neuronal excitability and maintaining equilibrium (Battista et al., 2012: see also, Battista et al., 2015).

After the eCBs produce their effects, it is believed that they are taken back up into neurons by an endocannabinoid membrane transporter (EMT). Back in the neuron, specific enzymes metabolize them. For AEA, the major enzyme is fatty acid amide hydrolase (FAAH), which is found in the postsynaptic neuron. For 2-AG, the enzyme is monoacylglycerol lipase (MGL), which is found in the presynaptic neuron.

Drugs that inhibit uptake of eCBs as well as FAAH inhibitors have been developed that can increase brain levels of anandamide in rodents and produce analgesia and benzodiazepinelike effects in vivo, making FAAH a possible target for pain and anxiety treatment.

So, what is the function of eCBs? It has been proposed that the endocannabinoid system is involved in the normal incentives elicited, for example, by good food or other pleasurable behavior. Abnormal forms of reward, either to natural substances or drugs, are associated with dysregulated eCB signaling (Covey, 2016). According to Parsons and Hurd (2015), "[i]mpaired eCB signaling contributes to dysregulated synaptic plasticity, increased stress responsivity, negative emotional states, and cravings that propel addiction. Understanding the contributions of eCB disruptions to behavioral and physiological traits provides insight into the eCB influence on

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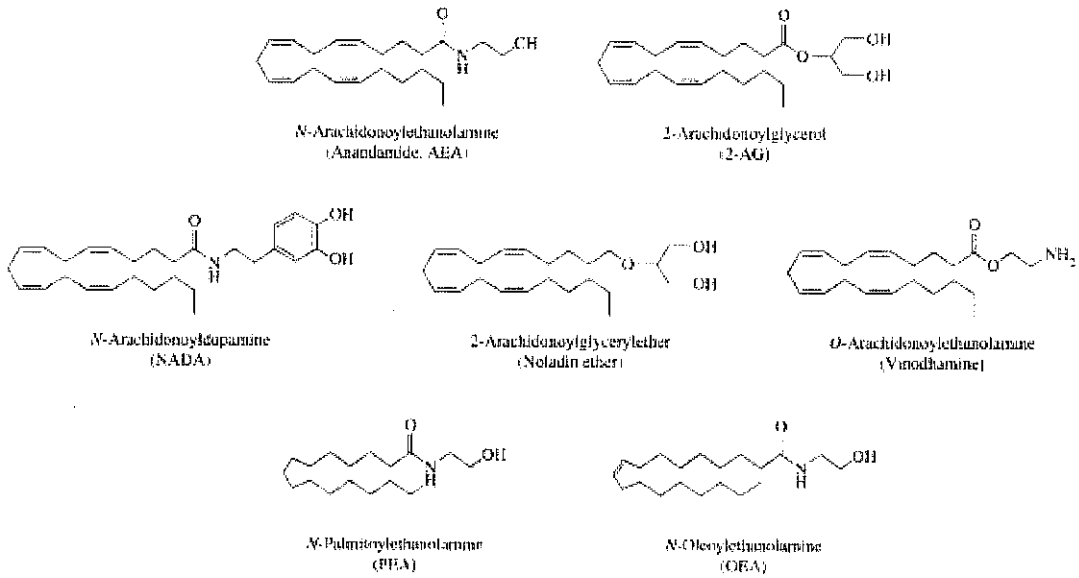

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PHARMACOKINETICS

THC

THC is usually administered in the form of a hand-rolled marijuana cigarette (called a "joint") or a pipe. In general, about one-fourth to one-half of the THC is actually available in the smoke. In practice, the amount absorbed into the bloodstream depends on the amount of THC, how deeply the smoker inhales, and how long the smoke is kept in the lungs. Estimates range from 5 to 60 percent of the available THC being absorbed into the body. Whatever the amount, absorption of THC from smoking is rapid and complete. Once absorbed, THC is distributed to the various organs of the body, especially those that have significant concentrations of fatty material, such as the brain. The behavioral effects occur almost immediately after smoking begins and correspond with the rapid attainment of peak concentrations in plasma. Because of its fast and thorough metabolism, only minor amounts of THC are ultimately eliminated. The initial metabolite, 11-hydroxy-THC, is comparably psychoactive and is quickly broken down into the inactive compound, 11-nor-9-carboxy-THC (THC-COOH).

Other methods of administration include "dabbing" and "vaping." Dabbing involves preparing highly concentrated THC by passing butane through a tube packed with dried cannabis ("blasting"). Once the butane evaporates, the remaining product, butane hash oil (BHO), can reach THC concentrations up to 80 percent. BHO is then vaporized by heating it (such as with a blow torch) and inhaled ("dabbed") through a water pipe apparatus ("oil rig"). Fires, explosions, and severe burns have been attributed to this process. In addition, little is known about the long-term risks of inhaling concentrated BHO or the by-products (solder, rust, benzene) produced from heating the titanium rod ("nail") that holds the BHO during vaporization.

Another practice similar to dabbing involves putting hash oil or marijuana in a vape device or e-cigarette (see Chapter 6). Some vape devices use regular marijuana, heated to a temperature sufficient to release the active ingredients—mostly THC and CBD—as an aerosol, while preventing actual combustion. Others use concentrates such as hash oil, which can contain toxic ingredients such as lighter fluid and pesticides. For people who have not smoked before, the high concentrations of THC from vaping hash oil requires caution (Giroud et al., 2015). This is especially important when vaping BHO, which tends to be much stronger than regular marijuana. Typical BHO is at least 60 percent THC, whereas most marijuana is around 12 percent (although some strains may be as high as 28 percent).

Because much of the THC taken into the body is stored in body fat, from which it is slowly released, very low, clinically insignificant amounts of THC in blood may be maintained for a considerable time after drug use ceases; this release can last from several days to about 2 weeks and even longer in chronic smokers and obese smokers (Huestis, 2005). Such a delay tends to prolong and intensify the activity of subsequently smoked marijuana, forming a type of "reverse tolerance" to the drug, where the persistent low levels are increased by subsequently smoked THC cigarettes.

Urine testing for THC focuses on identification of its inactive metabolite, carboxy-THC. Carboxy-THC is only slowly excreted, and its half-life in urine varies. In infrequent smokers (less than twice per week), urine samples will generally be positive for 1 to 3 days. In regular smokers (those who smoke several times per week), urine specimens can test positive for 7 to 21 days. In chronic smokers, daily use for prolonged periods of time can yield positive results for 30 days or longer. Thus, a positive urine test does not necessarily mean that a person was under the influence of marijuana at the time the urine specimen was collected; there is little or no correlation between the presence of carboxy-THC in urine and the presence of a pharmacologically significant amount of THC in the blood. This can become quite important in certain legal situations, such as charges of driving while under the influence of marijuana. Exposure to secondhand smoke will usually not result in a positive result for cannabinoid metabolites in urine.

According to data from the National Institute on Drug Abuse (2017), the average marijuana extract contains over 50 percent THC, with some samples exceeding 80 percent. It is difficult to know how much the typical consumer uses, that is, if they modify their consumption depending on the potency of the material. Because the potency in prior research might have been lower, results from past studies and current studies may differ (Cressey, 2015). A recent study by DiForti and colleagues (2015) found an association between high-potency (but not low-potency) cannabis and a greater, indeed triple, risk of psychosis.

In regard to potency and research, scientists have argued that the NIDA-supplied cannabis is not comparable to that used for medicinal or recreational purposes. The only legal source of this cannabis for scientific study is the University of Mississippi, which is the only institution that has exclusive permission from the federal government to grow the plant for experimentation. Until recently, the allowed amount for research was only 21 kilograms, but it has been increased to 650 kilograms (Carroll, 2015).

of these variables. The following sections summarize the major effects of cannabis and, where evidence is available, information on the specific actions of CBD, most of which comes from therapeutic applications.

Acute and Chronic Physiological Effects

Effects on the Cardiovascular System

Perhaps the most well-known cardiovascular effects of smoking marijuana are bloodshot eyes (due to dilation of the corneal blood vessels) and pupillary dilation. Smoking marijuana also elicits an initial dose-dependent increase in heart rate. Blood pressure might increase, decrease, or remain the same, depending on whether the user is standing, sitting, or lying down. Marijuana may increase the likelihood of stroke in those with other predisposing factors (Hackam, 2015). The first study (Wolff et al., 2015) to compare stroke characteristics and prognosis in younger patients (less than 45 years old) who do and do not smoke marijuana found that strokes produced by intracranial arterial stenosis were more likely to occur in those who did use the drug. This would be predicted from the cerebral vasoconstriction that is known to be elicited by cannabis. We know little about the consequences in older persons who might have compromised cardiovascular functions.

Effects on Respiration

Marijuana smoking involves repetitive, deep inhalation of unfiltered material, which is usually smoked as completely as possible in order not to waste any of the drug. So, it is no surprise that a single marijuana cigarette may be more harmful than a single tobacco cigarette in altering lung tissues and causing bronchial irritation and inflammation (Lutchmansingh et al., 2014). After controlling for tobacco use, however, there is no definitive evidence that marijuana smokers have an increase in lung cancer. This conclusion may still be premature because, in general, users smoke fewer marijuana cigarettes than nicotine, and the cohort of users may only now be reaching the age when such cancers appear. Turcotte and

colleagues (2016) discuss current information on the effect of cannabis, cannabinoids, and endocannabinoids on lung function.

Effects on Sleep

Several types of sleep disturbances have been linked to chronic cannabis use, such as trouble falling asleep, maintaining sleep, feeling groggy during the next day, and the like, particularly if use began before the age of 15. If use began after the age of 18, the only difficulty was in nonrestorative sleep (Grandner, 2014). Even in adults, however, chronic daily marijuana use is significantly associated with sleep difficulties (Conroy et al., 2016).

Effects on the Immune System

Given that CB2 receptors are found primarily in the immune system, it should not be surprising that long-term marijuana use is associated with a degree of immunosuppression, which might potentially render the smoker susceptible to infections or disease (Hegde et al., 2010). Currently, cannabinoid-induced immunosuppression does not seem to be involved in any diseases, although anti-inflammatory actions might be an important target in combating human disease (Chiurchiu et al., 2015).

Effects on Appetite, Nausea or Vomiting, and Gastrointestinal Disorders

One of the classic effects attributed to marijuana use is appetite stimulation, especially for sweet and fattening foods. This ancient association has been confirmed by modern research. THC and other CB1 receptor agonists stimulate appetite in test animals, even when the animals are sated (Seely et al., 2011). In wasting disorders, such as AIDS or cancer, cannabis may increase appetite and weight gain, but not more than the amount produced by other medications. It is possible that cannabis may actually regulate body weight, having no effect when weight is normal or excessive, but increasing it in those who are underweight. Alternately, the effect of the drug on body weight may be associated with long-term

versus short-term use, the presence of other drugs, or the competition between cannabis and food for brain sites that mediate reward (Sansone and Sansone, 2014).

Appetite stimulation has been used to clinical advantage. In 1981, *nabilone* (Cesamet), a synthetic derivative of THC and the first licensed cannabis medical product, was approved to treat nausea and vomiting associated with cancer chemotherapy. In 1985, *dronabinol* (Marinol), which is synthetic THC, was approved as an antiemetic for similar situations and, in 1992, approval was extended to stimulate appetite in wasting conditions, such as AIDS. In August 2017, Syndros was approved as the first dronabinol solution for oral use, making it easy to swallow and allowing the dosage to be titrated to clinical effect. Whether other components of cannabis have antiemetic properties has not yet been determined and may be worth investigation (Rock and Parker, 2016). A cannabinoid *antagonist, rimonabant* (Acomplia), was developed as a diet drug, but its safety was unacceptable and it was removed from the market (Lee et al., 2009). (These drugs are discussed later in this chapter.)

Recent anecdotal evidence suggests that *cannabinoids* may affect gastric emptying and colonic motility, and strong evidence exists of an intestinal anti-inflammatory effect (Esposito et al., 2013; Izzo et al., 2015; Naftali et al., 2014). Therefore, CBD seems to have the potential to target treatment of gastrointestinal tract disorders such as irritable bowel syndrome and inflammatory bowel disease in addition to its possible role in inhibiting colon cancers (Romano et al., 2014).

Acute and Chronic Psychoactive Effects

Subjective Effects

The psychological and psychiatric effects of THC vary with dose, route of administration, experience of the user, vulnerability to psychoactive effects, and the setting in which administration occurs. Users report an increased sense of well-being, mild euphoria, relaxation, and relief from anxiety. In an interesting side note, moderate use of marijuana by married couples was associated with less intimate partner violence (Smith et al., 2014). Sometimes anxiety is increased, which may be at least partly due to the perceived increase in heart rate. In general, the senses may be enhanced and the perception of time is usually altered. Often,

events seem especially funny, and laughter is easily elicited. Mundane ideas can seem profound and the loosening of associations and thought intrusions can produce an inflated sense of creativity. Illusions and hallucinations occur infrequently, possibly more at high doses.

Psychomotor Effects

Cannabis can produce impairments in coordination, perception, reaction time, and divided attention that persist for several hours beyond one's perception of the "high." This alone has obvious implications for the operation of a motor vehicle as well as impairments in performance in the workplace or at school. Driving under the influence of marijuana doubles or triples the risk of a crash. People driving under the influence of marijuana tend to compensate by driving slower, but, when the task intensity of driving increases, the driver becomes more impaired. Specifically, cannabis use increases lane weaving and impairs critical-tracking tasks, reaction time, and divided attention (MacDonald and Pappas, 2016). This increased risk is greatly potentiated by concomitant use of alcohol, even though guidelines for concomitant use have not been legislated. Doucette and coworkers (2017) offer a proposal to use an oral fluid assay to determine the degree of cannabinoid-induced driving impairment.

Rewarding Effects

It is not really known why marijuana is so rewarding. In humans, there is a range of THC doses that is pleasurable; below that there is no effect, above that, the reaction is unpleasant (Grilly and Salamone, 2012). Nonhuman primates will self-administer THC, AEA, and 2-AG (Justinova et al., 2011), substances that activate the mesolimbic dopaminergic reward system (Cooper and Haney, 2009). Barkus and colleagues (2011), however, found that intravenous injection of THC did not increase dopamine release in the brain of male volunteers, even though it was sufficient to elicit psychotic symptoms in the participants.

Filbey and Dewitt (2012) demonstrated that in abstinent marijuana users, marijuana cues activated reward neurocircuitry and the magnitude of activation was associated with the severity of problems related to marijuana use. In contrast, the intravenous administration of a synthetic CB1 agonist, Org-26828, to healthy

male volunteers produced drowsiness at low doses, but caused unpleasant effects of anxiety, paranoia, and hallucinations at higher doses (Zuurman et al., 2010).

Huestis and colleagues (2001) demonstrated in humans that a specific antagonist for cannabinoid receptors produced a dose-dependent blockade of marijuana-induced intoxication and tachycardia. This suggested that cannabinoid antagonists might be used to reverse cannabinoid intoxication in people who experience unpleasant reactions (for example, panic and psychosis) or to treat cannabis addiction, similar to the use of naloxone for opioid overdose or addiction (see Chapter 10). Although cannabis, even when it is the only drug ingested, produces numerous drug-related emergency room visits each year, it is not a lethal substance. Estimates are that a fatal dose would have to be 20,000 to 40,000 times the typically ingested dose (Levinthal, 2012). Moreover, even chronic use does not inevitably produce physical ill health. Laboratory measures of physical health (periodontal health, lung function, systemic inflammation, and metabolic health), as well as self-reported physical health status, showed that moderate cannabis use, even after 20 years, is not associated with physical health problems in early midlife, except for periodontal disease (Meier et al., 2016).

Cognitive Effects

Perhaps the best-known psychoactive effect of marijuana is that it produces memory impairment. THC impairs all stages of memory, including encoding, consolidation, and retrieval. The ability to focus attention and filter out irrelevant information is disrupted. Marijuana users' speech and presumably their underlying thought patterns become fragmented. Because of the distracting intrusions of other ideas, users forget what they or others have recently said. This difficulty in concentration impairs performance on many cognitive tasks. Furthermore, marijuana may also reduce the motivation to perform well. Even nabilone has been shown to cause impairments in attention and memory in computerized laboratory tasks in healthy male volunteers (Wesnes et al., 2010).

The memory-disrupting effects appear to be mediated by CB1 receptors in the hippocampus (Wise et al., 2009), perhaps by actions on mitochondrial CB1 receptors in that structure (Hebert-Chatelain et al., 2016). One large study of nearly a thousand marijuana users, as well as healthy controls for comparison, found that the drug was associated with abnormally low blood flow in virtually every area of the brain, but especially in the hippocampus, which might increase the risk of

the brain, but especially in the hippocampus, which might increase the risk of ultimately developing Alzheimer's disease (Amen et al., 2017). Long-term, heavy cannabis use in MS patients (with a mean duration of 27 years) may affect cognition beyond what might occur as a result of the disease itself (Honarmand et al., 2011; Pavisian et al., 2014). One intriguing finding is that the memory impairment produced by smoking marijuana may be inversely correlated with the amount of CBD in the product (Morgan et al., 2010).

Although cognitive deficits can persist for at least one month following discontinuation of heavy use, it is generally believed that only minimal effects are likely to persist. One study, however, has found that heavy cannabis users have smaller hippocampi and amygdalae than control subjects, and that this was associated with having a certain form of the CB1 gene (Schacht et al., 2012). Given the importance of these two structures for cognition, such long-term changes are troubling, especially considering that the mean age of the men and women in the study was between 27 and 28. These data are consistent with the findings of Meier and colleagues (2012), that people with comparable IQs at age 7, who were persistently diagnosed with cannabis abuse when they were teenagers, had statistically significant decreases in IQ by the age of 38. If heavy cannabis use began in adulthood, there was no change in IQ.

Effects on the Reproductive System and Pregnancy

In Western culture, marijuana is often reported to enhance sexual responsivity, whereas other cultures consider the drug to be a sexual depressant. This difference may be an example of the strong influence of expectation on cannabis's effects. But it is also possible that there is a dose-related mechanism in that low doses may enhance libido while higher doses depress it. Chronic use of marijuana by males can reduce levels of the hormone testosterone and reduce sperm count and viability (duPlessis et al., 2015). Reductions in male fertility and sexual potency, however, have not been reported. On the other hand, there is some evidence that smoking marijuana is associated with a mild increase in testicular cancer (Gurney et al., 2015). This is the most common malignancy diagnosed in young men between the ages of 15 and 45. In females, the levels of follicle-stimulating hormone and luteinizing hormone are reduced by the use of marijuana. Menstrual cycles can be affected and anovulatory cycles have been reported. All these actions reverse when drug use is discontinued.

Marijuana is the most widely used illicit drug during pregnancy and its use is increasing. Aside from recreational use, pregnant women are increasingly using marijuana to treat nausea, particularly during the first trimester of pregnancy, which is the riskiest period for deleterious effects of drug exposure to the fetus. Endogenous cannabinoids are present by day 16 of gestation, at the beginning of central nervous system development, when neural circuitry is forming. Moreover, the concentration of THC is increasing, not only in marijuana but also in other formulations, such as hash oil. Pregnant women, and those considering becoming pregnant, should be advised to avoid using marijuana or other cannabinoids either recreationally or to treat their nausea (Volkow et al., 2016).

THC freely crosses the placenta and is found in breast milk. Therefore, the developing brain is susceptible to cannabis during gestation and it would be expected to have some neurodevelopmental consequences. But the data are sparse and conflicting. While some reviewers conclude that cannabis increases the likelihood of preterm birth and small size for gestational age (Fantasia, 2017), others report only a small, nonclinically important drop in birth weight, with no difference even in preterm births or neurodevelopmental outcome for at least the first three years (Zhang et al., 2017). Although cannabis use does not appear to increase the incidence of birth defects (Mark and Terplan, 2017), one report concluded that newborns of women who smoked marijuana when pregnant may display mild, transient withdrawal signs, such as hyperactivity, reduced cognitive functioning, and changes in dopaminergic functioning (Metz and Stickrath, 2015).

The problems with information about the effects of cannabis and synthetic cannabinoids during pregnancy are that (1) the data are obtained from self-reports and (2) that it is often complicated by concurrent use of other drugs, including tobacco and alcohol (Orsolini et al., 2017). It has been reported that the majority of women reduce their consumption of or terminate cannabis use while they are pregnant (Mark and Terplan, 2017). In this regard, a survey of current cannabis use among pregnant women found that 35 percent of women were using cannabis when their pregnancy was confirmed and of those, 34 percent continued to use the drug, even though 70 percent believed that cannabis during pregnancy could be harmful. If a pregnant woman believed that cannabis was not harmful during pregnancy, she was more likely to use the drug (Mark et al., 2017). Lamy and colleagues (2017) tested the stool (meconium) of newborns to determine what the fetus ingested during the third trimester of gestation. They then compared the results with the self-reports of the mothers. The levels of cannabis metabolites were low and were not well correlated with maternal reports of cannabis use, whereas the levels of the

not well correlated with maternal reports of cannabis use, whereas the levels of the tobacco metabolite cotinine were highly correlated with maternal smoking reports. Recently, Kim and coworkers (2017) "developed and validated a specific and sensitive method for the simultaneous determination of THC, its metabolites, . . . and CBD in umbilical cord samples," which should provide a more accurate method for determining fetal exposure. There is a need to obtain more information on its gestational and postnatal effects (Grant et al., 2017).

Therapeutic Applications of Cannabinoids

According to a recent survey, in spite of minimal clinical evidence for such indications (see next section), a substantial number of people decrease their use of medications for pain, anxiety, migraines, and insomnia after starting medical cannabis use (Piper et al., 2017).

Nonpsychiatric Disorders

Effects on Pain and Spasticity

In both humans and animals, THC and cannabinoids have been reported to be analgesic, especially against pain resulting from persistent inflammation or neuropathic pain, an action distinct from that of opioids such as morphine (Boychuk et al., 2015). Patients using medical marijuana to control chronic pain reported a 64 percent reduction in their use of more traditional, opioid prescription pain medication (Boehnke et al., 2016), although clinical data are still scarce (Nielsen et al., 2017; Nugent et al., 2017). Efforts to develop a cannabis-derived analgesic agent for clinical use, however, are yet to be successful and there is a great deal of conflicting experimental results. One systematic review of randomized trials concluded that smoking marijuana was not efficacious for managing chronic noncancer pain (Deshpande et al., 2015). In contrast, compelling evidence exists that CBD can reduce sensations of painful burning, pins and needles, numbness, neuropathic pain, and other painful conditions (Jensen et al., 2015). Fine and Rosenfeld (2013) review the analgesic effects of cannabinoids, focusing on CBD.

Smoking marijuana may, however, specifically reduce spasticity-related pain in people diagnosed with multiple sclerosis (MS). An oral medication, *nabiximols*

people diagnosed with multiple sclerosis (MS). An oral medication, *nabiximols* (Sativex), is approved in Canada, New Zealand, and eight European countries for the relief of muscle spasms and poor sleep quality associated with MS as well as pain associated with end-stage cancer. Sativex contains THC and CBD in a 1:1 mixture, delivered in an oromucosal (mouth) spray. Patti and coworkers (2016) reviewed the efficacy of Sativex: 60 percent of patients reported efficacy, 26 percent discontinued the drug for lack of effectiveness, and 18 percent for side effects. The data suggest that any analgesic effect of cannabis may be due to the muscle relaxation as a result of its antispastic action rather than a direct analgesic action.

The American Academy of Neurology (AAN) supported nabiximols for MS pain and spasticity (Koppel et al., 2014) and recommended nabiximols and dronabinol for spasticity and central pain, and nabiximols for urinary disorders of MS as well (Hill, 2015). In contrast, Whiting and colleagues (2015) concluded that there was only moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity (see also Otero-Romero et al., 2016), and that there was only low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome.

Epilepsy

In the popular press, there are numerous uncontrolled clinical cases reporting medical marijuana as a treatment for epilepsy. Many of these are anecdotal accounts of children with refractory epilepsies, such as Dravet syndrome, Lennox-Gastaut syndrome (LGS), and Doose syndrome. Interest in the "Charlotte's Web" form of marijuana surged after its reported benefit in Charlotte Figi. The "Charlotte's Web" strain of medical marijuana has very little THC, with greater than a minimum 30:1 CBD-to-THC ratio (Kaur et al., 2016; Kolikonda et al., 2016; Saad and Joshi, 2015).

In 2016, several positive clinical studies were reported in conference abstracts. That same year, GW Pharmaceuticals announced positive results of the first randomized, double-blind, placebo-controlled Phase 3 clinical trial of its investigational medicine Epidiolex (CBD) for the treatment of LGS. In this trial, Epidiolex, when added as an adjunct to the patient's current treatment, significantly reduced the monthly frequency of drop seizures assessed over the entire 14-week treatment period compared with placebo ($p = 0.0135$). Epidiolex has

"Orphan Drug Designation" from the FDA for the treatment of LGS and Dravet syndrome. Devinsky and coworkers (2017) have recently reported positive results for cannabidiol in Dravet syndrome.

Neuroprotection

Cannabinoids and their derivatives have been postulated to possess neuroprotective effects following brain injury (Fernandez-Ruiz et al., 2012; Nguyen et al., 2014). This action is based on the ability of THC to inhibit glutaminergic transmission and reduce reactive oxygen intermediates, which may mediate neuronal damage after head injury. One synthetic cannabinoid derivative, however, dexanabinol, was not efficacious in the treatment of traumatic brain injury in humans (Maas et al., 2006).

Cancers

The use of marijuana to treat the nausea and vomiting, anorexia, and pain associated with cancer chemotherapy led to studies of possible antitumor effects of cannabis. McAllister and colleagues (2015) and Huang and colleagues (2015) reviewed the antitumor properties of CBD and discussed its potential beneficial effects on many types of cancer, including glioblastoma, breast, lung, prostate, and colon cancer. This may be an important advance beyond the symptomatic treatment of cancer-associated nausea, vomiting, and pain. Soderstrom and coworkers (2017) provide an extensive review of cannabinoids and cancer, emphasizing actions that are not mediated by CB receptors.

Glaucoma

In 2014, the American Academy of Ophthalmology (AAO) reiterated that it does not recommend the use of medical marijuana or other cannabis products to treat glaucoma, particularly when standard therapies are available and effective. The AAO used findings from an analysis by the National Eye Institute and the Institute of Medicine as the basis for its position. Reductions in intraocular pressure following medical marijuana use were short-lived.

Psychiatric Disorders

Alzheimer's Disease

In patients already diagnosed with Alzheimer's disease, up to 4.5 milligrams daily of oral THC daily showed no benefit in reducing neuropsychiatric symptoms in dementia, such as aggression and agitation, but it was well tolerated (Van den Elsen et al., 2015). In contrast, early work in animals has shown that CBD can reverse cognitive deficits (Booz, 2011). CBD may blunt beta-amyloid-induced neuroinflammation and may be a promising agent for reducing the neuronal loss seen in Alzheimer's disease (Esposito et al., 2007; Martin-Moreno et al., 2011). Results of preliminary experiments by researchers at the Salk Institute have indicated that THC and other constituents of cannabis may facilitate the elimination of amyloid beta from brain cells. Although these data came from neurons developed in the laboratory, the implications may promote new treatments for Alzheimer's disease (Currais et al., 2016).

Anxiety Disorders

One of the indications allowed for medicinal marijuana in some states is posttraumatic stress disorder (PTSD). Although there are some scattered reports that the drug may decrease symptoms of PTSD, definitive conclusions are premature because there is insufficient clinical trial data (O'Neil et al., 2017; Yarnell, 2015). Wilkinson and colleagues (2016) conclude that we do not have satisfactory information on the safety and efficacy of marijuana for the psychiatric conditions of Tourette's syndrome, PTSD, or Alzheimer's disease. Anxiety is positively associated with cannabis use or cannabis use disorder (CUD) in cohorts drawn from some 112,000 noninstitutionalized members of the general population of 10 countries (Kedzior and Laeber, 2014). Wilkinson and coworkers (2015) found that chronic marijuana use in war veterans actually worsened PTSD and was associated with more outbursts of violent behavior and alcohol use. Nevertheless, there is some evidence that cannabis has some therapeutic effect for social anxiety (Blanco et al., 2016), possibly by reducing negative emotional states in those with this disorder (Buckner and Schmidt, 2009).

The DEA recently approved the first U.S. clinical trial to develop the marijuana plant into a prescription medicine to treat PTSD symptoms. The randomized controlled trial—sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), a nonprofit organization dedicated to alternative medicine—will document the effects of smoked marijuana on 76 war veterans who have chronic, treatment-resistant PTSD. With DEA approval, the study has been given the green light from every relevant federal agency, including the Food and Drug Administration, the National Institute on Drug Abuse, and the Public Health Service. According to MAPS, the study started in 2016, and as of April 2017, had 12 subjects.

In contrast to marijuana, and perhaps because of its antagonistic action, early evidence strongly supports CBD as a treatment for a variety of anxiety disorders, including generalized anxiety disorder (Sarris et al., 2013), panic disorder (Soares and Campos, 2017), and social anxiety disorders (Bergamaschi et al., 2011; see also Blessing et al., 2015). But few studies have investigated chronic CBD dosing or compared CBD with drugs known to also be effective, such as benzodiazepines. One interesting aspect of this issue is the recent report of a genetic variant that influences the synthesis of the endogenous cannabinoid, anandamide (Dincheva et al., 2015). That is, some people (as well as mice) have a mutation of the gene that is responsible for making the enzyme FAAH, which deactivates anandamide. In other words, anyone with this mutation has less of the FAAH enzyme and, consequently, more anandamide. This suggests that such individuals may be generally less anxious or less likely to find cannabis as rewarding than people who naturally have more of the FAAH enzyme and less anandamide.

Schizophrenia

There is compelling epidemiological evidence that cannabis is a risk factor for the onset of psychosis (Hamilton, 2017; Wilkinson et al., 2015). It has long been known that schizophrenia patients have a greater history of cannabis abuse (25 percent) than people in the general population (4 percent). As early as 1958, a published study described psychoticlike behavior in healthy volunteers after a single ingestion of cannabis, and it has been reported that up to 15 percent of cannabis users experience acute psychotic symptoms. In 1987, a comprehensive review of over 45,000 Swedish military conscripts found that those who consumed high amounts of cannabis (used more than 50 times) by the age of 18 years were 6 times more likely

prognosis than schizophrenia cases in general (Manrique-Garcia et al., 2014). Furthermore, continued use of cannabis after onset of psychosis was associated with more relapses compared with both discontinued use and never having used cannabis at all (Schoeler et al., 2016a, 2016b; see Andrade, 2016, for a review). One study found that cannabis users at baseline had lower body mass index, smaller waist circumference, lower diastolic blood pressure, and more severe psychotic symptoms than nonusers; all these parameters decreased in patients who discontinued their cannabis use after the first assessment (Bruins et al., 2016), which suggests some metabolic interactions of cannabis with either schizophrenia or, perhaps, antipsychotics.

Possible causes for the relationship between early onset cannabis use and psychosis are controversial. One factor is the increased potency of cannabis (DiForti et al., 2015). During the last 20 to 30 years, the percent of THC in all parts of the marijuana plant has increased, with some reports of up to 18 percent or more, compared to past levels of 3 percent. It is not known whether or not cannabis users modify their behavior if the potency increases, for example, by smoking less, or changing the way they inhale. There is some data showing that users with more experience may alter their intake, depending on how strong they think the material is, but they are not capable of making accurate adjustments when potency varies or on overcoming the negative emotional effects of the drug (Freeman, et al., 2014; van der Pol, et al., 2014).

Some studies suggest that the risk of developing schizophrenia is an impetus for the onset of cannabis use (Gage et al., 2016). Other findings suggest that a small part of the association between schizophrenia and cannabis is due to a shared genetic etiology (Power et al., 2014), although a common genetic risk could not explain the entire association with symptoms of psychosis (Nesvåg et al., 2017).

Another factor involved in cannabis-induced psychosis may be the concentration of CBD. Leweke and colleagues (2012) report that this component of cannabis reduces psychotic symptoms in patients with acute schizophrenia. Similarly, another study found that healthy people had fewer psychotic reactions to intravenous THC if they were pretreated with CBD (Evins et al., 2012). Englund and colleagues (2013) also found that in normal volunteers, CBD inhibited psychotic and paranoid symptoms and even improved the memory impairment produced by THC. Indeed, CBD appears to have therapeutic potential in the treatment of schizophrenia as well as in the acute treatment of THC-induced psychosis

does not promote psychiatric problems. Frequent use, however, may increase the likelihood of depression and suicidality (Agrawal et al., 2017). At the same time, among people with mental illness, reporting at least weekly use, the rate of cannabis use was especially high for those with bipolar disorder, personality disorder, and, perhaps not surprisingly, other substance use disorders, such as alcohol (Blanco et al., 2016; Lev-Ran et al., 2013; Weinberger et al., 2016). In bipolar patients, recent studies have noted that cannabis use preceded the onset of mania (Gibbs et al., 2015; Tyler et al., 2015). Current cannabis users were less likely to have periods of recovery and remission and more likely to have recurrence, relapse, and attempted suicide; previous users' patterns closely resembled the patterns of those who never used cannabis (Zorrilla et al., 2015).

SYNTHETIC CANNABINOID AGONISTS OF ABUSE

In 1964, after THC was determined to be the active ingredient of *Cannabis sativa*, efforts were made to develop synthetic cannabinoids (SC) for possible therapeutic applications. By 1985, this had been accomplished and *dronabinol* (Marinol) was approved in the United States as an antiemetic drug. Several other agents that are chemically similar to THC have also been produced, notably *nabilone* (Cesamet) and HU-210 (synthesized at the Hebrew University in the 1960s). Nabilone is almost as potent as THC and is the only THC analog that has ever been approved as an antiemetic in the United States. HU-210 has not been approved, mainly because it is 100 to 800 times as potent as THC (Seely et al., 2011).

Additional SC compounds that differ chemically from THC were also synthesized. Chemists at the drug company Pfizer developed a group of drugs known as *cyclohexylphenols* (CP). These include substances designated as CP-50,556-1 and CP-47,497, and a related form, (C8)-CP-47,497, all of which are 30 times more potent than THC. Perhaps the newest cyclohexylphenol is NE-CHMIMO (Angerer et al., 2016), which has been found along with 5F-ADB (also known as 5F-MDMB-PINACA, another synthetic cannabinoid) in a so-called herbal mixture branded as "Jamaican Gold Extreme."

A third group of related drugs is categorized as aminoalkylindoles (AAI). This includes a drug called *pravadoline* and similar compounds, such as WIN-55212–2,

developed by Sterling Drug Company. These drugs have a high affinity for both types of cannabis receptors, produce effects similar to those of THC in laboratory animals, and are blocked by cannabinoid antagonists. Nearly 20 years ago, John W. Huffman, a research chemist at Clemson University, created three of these AAIs, designated JWH-018 (1-pentyl-3-(1-naphthoyl)-indole), JWH-073, and JWH-015. These drugs have different binding affinities to the two CB receptors, but generally have similar pharmacological effects as THC, with JWH-018 having the greater relative potency (Seely et al., 2011).

Last, a fourth group of compounds that act at CB receptors, called *benzoylindoles*, include the substances AM-694 and RCS-4 (Fattore and Fratta, 2011). (For a more detailed list of chemical subdivisions, see Rosenbaum et al., 2012.)

Current Abuse

In the early 2000s, several SC compounds became available and were sold widely by "head shops" and convenience stores as well as through Internet vendors. By 2007, these compounds gained the attention of U.S. authorities. Generically called "spice" as well as other names,[1] these products are usually sold as dried leaves, resin, or powder, and without age restriction (Papanti et al., 2013; Rosenbaum et al., 2012). (See Seely et al., 2011, for a list of the herbs that are used in these products.)

The process by which spice is manufactured was compellingly described by the *New York Times* reporter Alan Schwarz (2015). After production in China, SC drugs are transported to U.S. wholesalers in the form of powder, packed in containers, and stamped as fertilizer or industrial solvents. At these sites, the powder is dissolved in alcohol or acetone, sprayed on plant material that can be smoked, and then packaged in metallic bags, which often contain the warning "Not for human consumption." Sometimes the plant material is prepared in containers that held animal feed, in cement mixers, or in other unprotected locations, which could be contaminated with hazardous substances, mold, and the like.

The chemicals are also now available as liquid cartridges used in electronic cigarettes (Castellanos and Gralnik, 2016). Typically, about 3 grams of vegetable matter are mixed in a synthetic cannabinoid package, which can be smoked or drunk as an infusion. The vegetable matter (the "herbals") in these preparations is

not psychoactive; it is the synthetic drugs (the "spice") that produce the psychoactive effects.

Several factors make treatment of SC abuse difficult. There is no antidote yet, which means that no matter how intense or unexpected the reactions, the only available remedies are intravenous electrolytes and other basic medical support. Because the symptoms of intoxication can also be elicited by other types of abused stimulants or hallucinogenic drugs, it is not easy to diagnose the syndrome produced by SC agents, especially in someone who has not used them before. The problem in identifying SC intoxication is made even more difficult because there are no quick laboratory assays to confirm the presence of the drug. There is no standard urine screen for SC agents and exposure can only be verified by complicated analyses in specialized laboratories (Trecki et al., 2015). Furthermore, even the metabolic products of these substances may be psychoactive and elicit some of the symptoms (Seely et al., 2012). The difficulty of determining the active ingredients in spice products is also due to the addition of natural substances, such as tocopherol (Vitamin E) and some agents, such as nicotine, that might be stated as an ingredient, but are not actually present. In an effort to avoid federal and state prohibitions, additives are frequently changed. Furthermore, it takes time for various laboratories to calibrate and verify their in-house techniques, even after the initial agent and its metabolites are identified (Papanti et al., 2013; Trecki et al., 2015).

In summary, these drugs have gained worldwide popularity because they produce psychoactive effects; may still be legal, are easily available, and cheap; and are still difficult to detect, even though their negative psychoactive effects are now generally well known (Lauritsen and Rosenberg, 2016). Several European countries have banned these compounds. In the United States, synthetic cannabinoids have been classified as Schedule I compounds and are now banned in all states.

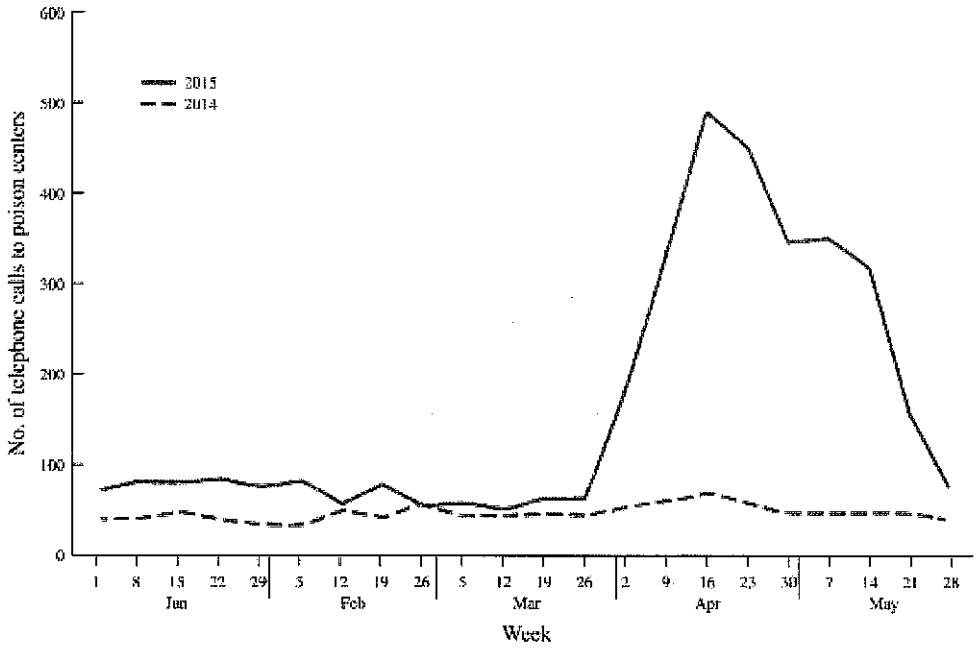
Pharmacological, Physiological, and Psychoactive Effects and Toxicity

In general, the basic pharmacology and pharmacokinetics of synthetic cannabinoids is unknown. Likewise, effects in pregnancy have not been reported. Presley and coworkers (2016) review what little is known about their metabolism in the body.

Miliano and coworkers (2016) review the rewarding effects of these cannabinoid agonists as dopaminergic signaling agents in the nucleus accumbens. Cooper (2016) reviews the adverse effects of both acute intoxication as well as long-term abuse and subsequent withdrawal problems.

According to Papanti and colleagues (2013), "[t]he available evidence suggests that SCs can trigger the onset of acute psychosis in vulnerable individuals and the exacerbation of psychotic episodes in those with a previous psychiatric history" (379). Significantly, more symptoms ($p = 0.03$) were reported by respondents seeking treatment for SCs than for cannabis (Winstock and Barratt, 2013). Clinical symptoms include excited delirium, acute kidney injury (AKI), seizures, psychosis, hallucinations, cardiotoxic effects, coma, and death. Deaths from SC use have ranged from 13 to 56 years of age (Trecki et al., 2015; see their summary table of major episodes and outbreaks of SCs).

Shalit and colleagues (2016) compared SC users to cannabis users. Figure 9.6 provides some information about the increase in adverse reactions to these compounds. SC users were generally younger males who had greater severity of psychotic symptoms at admission, were more likely to be admitted by criminal court order, and required longer hospitalization periods in comparison to cannabis users. Cited motives for SC use included curiosity or experimentation (91 percent), a desire to feel good or get high (89 percent), to relax (71 percent), and to get high without risking a positive drug test (71 percent) (Bonar et al., 2014).



Advokat/Comaty/Julien, *Julien's Primer of Drug Action*, 14e,
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FIGURE 9.6 A line graph comparing the number of weekly telephone calls to poison centers in the United States reporting adverse health effects related to synthetic cannabinoid use from January to May 2014 and the same period in 2015.

[Data from Law et al., 2015.]

As noted, there is no pharmacologically specific antidote for these substances, especially because the actual contents are usually unknown. Spice blends do not contain CBD and the use of CBD as an antidote to spice intoxication has not yet been reported. In addition to supportive care, benzodiazepines may be helpful for anxiety and agitation caused by spice intoxication.

Tolerance and a cannabinoid withdrawal syndrome have been reported. Withdrawal symptoms are typical of cannabis withdrawal, namely, internal unrest, sweating, drug craving, nightmares, tremor, palpitations, nausea, and vomiting. Psychotic symptoms may be elicited in normal individuals, and recovered psychotic patients may relapse. Gastrointestinal reactions are common, and several cases of AKI from these agents were reported across the United States (Murphy et al., 2013). Five of the patients needed hemodialysis. There was no single brand associated with all the cases, but a new, previously unreported fluorinated agent was discovered, methanone (XLR-11), which was a potent CB agonist. Coma and suicide have been reported. In the United States, for example, two adolescents died after

neighborhood consumed a synthetic cannabinoid drug that produced intoxicated behavior likened to a "zombie" outbreak. The substance they took was the "incense" compound AK-4724 Karat Gold, that is, AMB-FUBINACA or MMB-FUBINACA, which stands for methyl 2-(1-(4-fluorobenzyl)-1H-indazole-3-carboxamido)-3-methylbutanoate). In the serum or whole blood of eight individuals, the metabolite concentrations ranged from 77 to as high as 636 nanograms per milliliter (Adams et al., 2017).

Associated Press

A three gram package of K_2, a synthetic cannabinoid.

CANNABIS TOLERANCE, WITHDRAWAL, ADDICTION, AND DEPENDENCE

Experienced users of marijuana often report that they become more sensitive to its psychoactive effects (sensitized) rather than less (tolerant) with continued use. That is, they become "high" more quickly. However, tolerance to cannabis routinely develops in laboratory studies. This difference between experimental and "real-world" exposure is believed to be due to several factors. First, novice users have to learn how to get enough of the smoke into the lungs to provide a sufficient THC dose. Second, new users have to learn to be aware of the subjective effects of the drug. Third, because the drug accumulates in fat tissue, regular smokers have some residual amount of THC in their bodies, which increases the total amount with each cigarette, producing a quicker "high." Nevertheless, tolerance does occur to

cannabis. Some degree of tolerance results from learning how to adapt to the drug's disruptive effects. Rodent studies had shown that CB1 receptors were downregulated after chronic cannabis exposure, which would also mediate tolerance. Hirvonen and colleagues (2012) have shown reversible and regionally specific downregulation of CB1 receptors in cortical brain regions of human subjects who chronically smoke cannabis. Downregulation correlated with years of smoking and receptor density returned to normal after about four weeks of monitored abstinence.

Withdrawal symptoms include irritability, anxiety, marijuana craving, disrupted sleep and strange dreams, anger and aggression, depressed mood, restlessness, decreased appetite, and weight loss. Less common symptoms include chills, headache, physical tension, sweating, stomach pain, and general physical discomfort (Vandrey and Haney, 2009). Symptoms begin within 48 hours after drug use stops and last at least 2 days, usually about 7 to 10 days, and perhaps longer; electroencephalography (EEG) changes associated with withdrawal persist for at least 28 days. Although withdrawal from cannabis has been compared to recovering from the flu or similar to nicotine withdrawal, the intensity, as with other drugs of abuse, depends on the severity of the dependence. The greater the dependence, the more severe the withdrawal syndrome, and the more likely that relapse will occur (Allsop et al., 2012). As would be expected, reinstituting marijuana use relieves withdrawal discomfort.

Originally thought to be a relatively benign and infrequent occurrence, cannabis dependence occurs in about one of every ten persons who start smoking the drug and is a common reason for admission to a drug treatment program (Benyamina et al., 2008; Cooper and Haney, 2009; Elkashef et al., 2008). When cannabis users were asked to rate the effects of their own use as positive, neutral, or negative, they gave overwhelmingly negative ratings of the effects that cannabis had on their social life (70 percent), their physical health (81 percent), their cognition (91 percent), their memory (91 percent), and their career (79 percent) (Elkashef et al., 2008). It has been estimated that 13 million individuals globally have an addiction to cannabis, with relapse rates comparable to those of other substance use disorders (Lorenzetti et al., 2016). The DSM-5 now includes a designation of *Cannabis Use Disorder* (CUD), which can be diagnosed as mild, moderate, or severe.[2]

MacDonald and Pappas (2016) present a very compelling case for concern regarding cannabis addiction. They note that increasing decriminalization, legalization, and medicalization of cannabis in many states will most likely increase

specific circumstances, but its effects can be overcome with higher doses of cannabis (Haney et al., 2015; Vandrey and Haney, 2009). According to Martinez and Trifilieff (2015), research is now being conducted to develop a cannabinoid agent that would only partially block the CB1 receptor such that it would decrease the subjective effects of cannabis, but avoid the negative side effects produced by the antagonist rimonabant.

Results of studies in animal models have shown that THC, acting on the CB1 receptor, influences both GABA and glutamate transmission. This has prompted assessment of drugs that produce their effects through these systems. *Gabapentin* is an antiepileptic and analgesic for neuropathic pain. While its mechanism of action is unclear (it binds poorly to GABA receptors, even though its structure is similar to GABA), it was found to increase GABA biosynthesis. Gabapentin had some positive effects in a clinical trial (1200 milligrams per day) although the dropout rate was high. A larger clinical trial, conducted at the Scripps Research Institute, completed data collection in May 2016.

N-acetylcysteine (NAC) is an over-the-counter supplement that is thought to restore the normal glutamate activity that is disrupted by chronic drug use. A recent clinical trial investigating NAC administration (1200 milligrams twice daily), in combination with the behavioral treatment of contingency management, showed that subjects receiving NAC were more likely to reduce their cannabis consumption compared to contingency management alone. A multisite trial of NAC for the treatment of cannabis dependence was completed in July 2016. So far, gabapentin and NAC appear to hold some promise, although the outcome of these treatments has not yet been fully evaluated (Gorelick, 2016; Sherman and McRae-Clark, 2016).

The potential role for CBD in a variety of chemical addictions has been recognized. Prud'homme and coworkers (2015) reviewed the antiaddictive potential of cannabidiol in opioid, cocaine, and methamphetamine dependence as well as in tobacco and cannabis dependence. Morgan and coworkers (2013) in a small study also noted a 40 percent reduction in the number of cigarettes smoked. As a CB1 antagonist, the rationale for CBD antagonism of THC effects is obvious.

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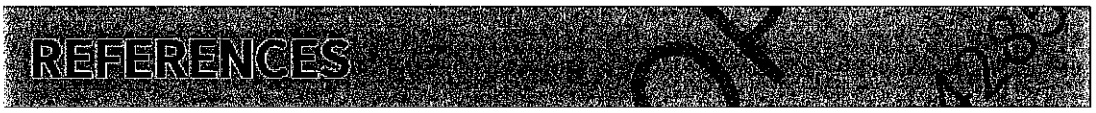
STUDY QUESTIONS

1. Summarize the history of cannabis.

2. What are the endocannabinoids? How do cannabis and the endocannabinoid system work?
3. What are the major acute and chronic physiological effects of cannabis on the body?
4. What are the cognitive effects of cannabis?
5. What are the psychological/psychiatric effects of cannabis?
6. Discuss evidence regarding current and possible future medical uses of THC and CBD. Should therapeutic uses be pursued?
7. Should cannabis be legalized for either medical or recreational use? If so, how should it be regulated or restricted?
8. What are synthetic cannabinoids? Where did they come from and what are their effects?
9. What pharmacological approaches are being taken to treat cannabis abuse?



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