Donald E. Greydanus, Gabriel Kaplan, Dilip R. Patel, and Joav Merrick (eds.)
Substance Abuse in Adolescents and Young Adults

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Substance Abuse in Adolescents and Young Adults

A Manual for Pediatric and Primary Care Clinicans

Edited by
Donald E. Greydanus, Gabriel Kaplan, Dilip R. Patel,
and Joav Merrick

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Dedication

Donald E. Greydanus. I dedicate this book to my parents – John S. and Margaret E. Greydanus, who sacrosanctly and sacerdotally taught me joie de vivre apart from caustic chemicals. From my loving parents, I learned nam et ipsa scientia potestas est. Requiescat in pace cum Deo.

Gabriel Kaplan. I dedicate this book to my parents Drs. Ana and Alberto Kaplan who have not stopped helping patients yet; and to my children Aaron, Yonatan, Ilan, and Arielle who will start helping patients soon.

Dilip R. Patel. I dedicate this book to my lovely wife, Ranjan, and wonderful son, Neil, for their years of love and support.

Joav Merrick. I dedicate this book to my wife and children for their support.

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Foreword

Adolescence is the life stage in which experimentation with substance abuse – especially alcohol, cannabis, and nicotine – usually begins. For most young people, trying alcohol and other drugs (including prescribed medications) is unlikely to result in long-term harm, but immediate risk is ever present, even on a single occasion. Unfortunately, accidents and violence, mental impairment, legal issues, unwanted sexual activity, damaged reputation, missing study or work, or on rare occasions, even death can result.

Ongoing substance abuse is particularly concerning, with complications including mental health problems (in particular anxiety, depression, and sleep disorders), infections with blood-borne infections, damage to organs (i.e., liver, heart, and brain), and increased risk of cancers as well as other serious health conditions.

It is therefore timely to focus on what is currently happening in this often vexing and complex area of adolescent/young adult health care. Substance abuse does not occur in isolation – it is mediated by an amalgam of individual, interpersonal, and societal factors. Predictors for initiation of substance use in adolescence, for example, include intrauterine assaults and genetic predispositions, temperament and personality, familial substance abuse, family conflict, and poor parenting. Some populations of young people are particularly at risk.

Fortunately, much is also known about factors protecting against risk behaviors, such as a warm, nurturing parenting style with judicious monitoring of behavior and fair rule setting, especially in the vulnerable early teenage years. Adolescents yearn for social acceptance and a sense of belonging and are less likely to engage with drugs when they feel supported and cared about as well as being well connected to family, school, and (hopefully) non-drug-taking peers. Contemporary treatment approaches, whether psychopharmacological or psychotherapeutic, reflect these new understandings.

Clinicians dealing with young people not uncommonly feel poorly equipped to inquire about drug taking or to know how best to respond if such disclosures are forthcoming including where to turn for help. There is evidence in Australia, for example, that doctors are not taking up opportunities to target problematic alcohol and tobacco use, a situation that is likely to be true in other countries as well. This practical manual sets the scene by providing up-to-date, evidence-based information in support of optimal clinical practice. A wide variety of aspects of substance

abuse are covered, and I congratulate the editors and authors for developing this treatise on such an important and timely topic.

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Abbreviations

2-AG	2-arachidonoyl glycerol
5-Me-DIPT	5-methoxydimethyltryptamine
AAS	anabolic-androgenic steroids
ADHD	attention-deficit/hyperactivity disorder
AEA	arachidonoyl ethanolamide
AmED	alcohol mixed with an energy drink
AMT	alpha-methyltryptamine
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
ATP	adenosine triphosphate
AUD	alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
BAC	blood alcohol concentration
BD	1,4-butanediol
BDNF	brain-derived neurotrophic factor
BI	brief intervention
BMI	brief motivational intervention
BPD	bipolar disorder
BTCP	1-bensothiophenyl cyclohexylpiperidine
BZP	benzodiazepine
BZP	benzylpiperazine
CAGE	cut down, annoyed, guilty, eye opener
CB	cannabinoid
CBC	complete blood count
CBD	cannabidiol
CBG	cannabigerol
CBT	cognitive behavioral therapy
CD	conduct disorder
CM	contingency management
CNR1	cannabis receptor-1 gene
CNS	central nervous system
CNV	copy number variations
COI	cost of illness
COPD	chronic obstructive lung disease
CRA	community reinforcement approach
CRH	cortisol-releasing hormone
CSF	cerebrospinal fluid
CT	computerized tomography
CUD	cannabis use disorder
DA	dopamine

DArgic	dopaminergic
DAST	Drug Abuse Screen Test
DAT	DA transporter
DHEA	dihydroepiandrostenedione
DMT	N, N-dimethyltryptamine
DPH	diphenhydramine
DXM	dextromethorphan
ECG	electrocardiogram
EPO	erythropoietin
FAS	fetal alcohol syndrome
FHS	follicle stimulating hormone
GABA	γ-aminobutyric acid
GAD	generalized anxiety disorder
GBL	gamma butyrolactone
GHB	γ-hydroxybutyric acid or gamma hydroxybutyrate
GI	gastrointestinal
GWAS	genome-wide association studies
HCG	human chorionic gonadotropin
HDAC	histone deacetylase
hGH	human growth hormone
HPA	hypothalamic-pituitary axis
HTG	hypertriglyceridemia
IM	intramuscularly
IUGR	intrauterine growth restriction
IV	intravenous, intravenously
LH	luteinizing hormone
LSD	lysergic acid diethylamide
LTD	long-term depression
LTP	long-term potentiation
MAO	monoamine oxidase
MAS	mixed amphetamine salts
MBDB	N-methyl-1,3-benzodioxolylbutanamine
MCD	meso-corticolimbic dopamine
mCPP	meta-chlorophenylpiperazine
MDA	methylenedioxyamphetamine or 3,4-methylenedioxyamphetamine
MDD	major depressive disorder
MDEA	methylenedioxyethylamphetamine or 3,4-methylenedioxy-N-ethylamphetamine
MDFT	multidimensional family therapy
MDMA	3,4-methylenedioxy-N-methylamphetamine or 3,4-methylenedioxymethamphetamine
MDPV	3,4-methylenedioxypyrovalerone

MeOPP	1-(4-methoxyphenyl)piperazine
MET	motivation enhancement therapy
MI	motivational interviewing
MMT	methadone maintenance treatment
MRI	magnetic resonance imaging
MXE	methoxetamine
NAC	N-acetylcysteine
NAc	nucleus accumbens
nAChR	nicotinic-subtype acetylcholine receptors or nictotinic cholinergic receptors
NAS	neonatal abstinence syndrome
NMDA	N-methyl-D-aspartate
NMUPD	nonmedical use of prescription drugs
NRT	nicotine replacement therapy
OCD	obsessive compulsive disorder
OROS-MPH	osmotic-release methylphenidate
OTC	over-the-counter
P2P	phenyl-2-propanone
PCP	phencyclidine
PDV	physical dating violence
PET	positron emission tomography
PFC	prefrontal cortex
PGB	pregabalin
PMA	paramethoxyamphetamine
PMK	3,4-methylenedioxyphenylpropan-2-one
PPD	postpartum depression
PTSD	posttraumatic stress disorder
QALY	quality-adjusted life year
RP	relapse prevention
SARMs	selective androgen receptor moderators
SBIRT	screening, brief intervention, and referral to treatment
SID	substance-induced disorder
SIDS	sudden infant death syndrome
SNP	single nucleotide polymorphism
SNRI	serotonin-norepinephrine reuptake inhibitor
SPECT	single-photon emission computed tomography
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
SUD	substance use disorder
TB	tuberculosis
TFMPP	trifluoromethylphenylpiperazine

THC	tetrahydrocannabinol
TPP	tegmental pedunculo-pontine
UDS	urine drug screen
VMAT	vesicular monoamine transporter
VPA	valproic acid
VTA	ventral tegmental area
WTP	willingness to pay

1 Introduction: Substance abuse in adolescents and young adults

Donald E. Greydanus, Gabriel Kaplan,
Dilip R. Patel, and Joav Merrick

Cannabis sativa and Papaver somniferum: Plants of Paradise that produce a vicious viniculum between ancient and modern homo sapiens:

> "On a bright morning they have fixed,
> To seek the plain that southward lies,
> Then from her task of twisting hemp,
> See dancing through the mart she hies"
>
> – She King, *Book of Ancient Poetry*, China, 2350 BCE

Homo sapiens sapiens emerged over 200,000 years ago and the flexuous, precarious journey of this species is nebulous, since writing only developed in southern Mesopotamia in the 4th millennium BCE (1,2). One aspect about these early humans that seems clear is they possessed a predatory, puerile central nervous system wired for seeking pleasure and foudroyant experiences. Perhaps the first recorded incident of humans seeking ultimate joy was the willingness to receive knowledge that would lead to happiness, as found in the Genesis 3:6 account of Eve and then Adam (in Hebrew *ha-adam*, or "mankind") consuming the forbidden fruit (in Hebrew *p'ri*) from the tree (in Hebrew *etz* or *Ha-etz*) of the knowledge of good and evil. They failed to first partake of the fruit (in Hebrew *ruach,* or spirit that provides eternal life) from the tree of life, and the consequences were disastrous for them, and for others, in this recording of the Fall of Man because a Cadmean curse resulted. They, of course, did not appreciate the tenacious puissance of consuming the wrong product; indeed, seeking and partaking of "fruits" or various epinosic and edacious chemicals, including those from natural plants, for various levels of joy and avoiding healthy plants has proved to be cimmerianly cataclysmic for human beings ever since.

There are many hallucinogenic and euphoria-inducing plants that have been available to humans for thousands of years. Some of them include *Datura stramonium, Datura candida, Amanita muscaria, Atropa belladonna, Rivea corymbosa, Pancreatium trianthum, Hyoscyamus niger, Erythroxylon coca, Papaver somniferum*, and many others. Each has induced its own unique jeremiad with promises of joy that end as an oubliette with a trap door of addiction and potential death. However, one could speculate that one of the most classic apolaustic drugs was the marijuana plant, which has been smoked for unknown millennia. The first worn fabric may have been woven from the hemp plant and dates back to 7,000–8,000 BCE, while use of hemp seeds as food has been noted in China by 6,000 BCE (3,4).

The first classifier of medicinal herbs was the Chinese emperor Shen-Nung (2737 BCE), and there is a classic painting of this emperor holding leaves of Ephedra (*ma-chuang*) (5). Humans turned to what was around them and found plants that proved useful for improving health as well as inducing euphoria. Shen-Nung, the red emperor who is the father of Chinese medicine, taught his Chinese subjects to grow *ma* (hemp) to make hempen cloth and, as noted, it was later used as a food product (6). His classic work, *Pen Ts'ao*, became a *Materia Medica* on various products, including the *dioecious cannabis* (4). Even today cannabis can be part of food products for humans and animals (7).

The hemp plant probably came from the Himalayas to ancient China and later to the entire world. The Hindu sacred text *Arthava-Veda* refers to cannabis as "Sacred Grass" and lists it as one of its five sacred plants; cannabis was used as offerings to the Hindu god Shiva, and was used as medication in India as early as 1200 BCE (3). Herodotus writes of the use of cannabis by the Scythians in 430 BCE (8). A tomb was found in China that contains marijuana and dates back to 700 BCE (9). The consummate Chinese cognoscenti, Confucius (551–479 BCE), compiled Chinese classics that included citations about cultivating and consuming cannabis crops.

Hallucinogenic-huffing bowls have been found in various parts of the world that are over 2,500 years old. Historians tell us of the Ebers Paprus (1550 BCE) from ancient Egypt, which was a 110-page scroll recording of over 700 formulas and remedies of mineral, vegetable, and animal origins (10,11). The history of opium poppy seed consumption dates back at least to ancient Egypt; the opium poppy seed was used as a food product long before its narcotic and soporific effects were fully appreciated (12). Athletes of the ancient Olympics (776 BC–393 AD) were known to consume various chemicals to aid in victory, and these chemicals included mushrooms, figs, and opioids that contained stimulants such as strychnine (13).

Ale is one of oldest liquids produced by humans, dating back to the 5th millennium BCE; beer dates back to at least 3000 BCE (14). The Old Testament notes that wine "gladdens" the heart (Psalm 104:15) but also warns of the dangers of overuse of alcohol (Proverbs 20:1, 10th century BCE), including poverty, strife, and injustice (Proverbs 23:20–21; 23:29–30; 31:4–5). Wine was prominently mentioned in the New Testament in the first century AD, such as its use at weddings (John 2:3) or association with drunkenness and debauchery (Ephesians 5:18). Moderation in wine drinking was also linked to improved health (1 Timothy 5:23).

The pioneer of surgical anesthesia was Hua Tue (190 AD), who used a formula called *ma-fei-san* (bubbling wine) that most likely contained medical cannabis (9). In the Roman civilization, the Greek physician to the Romans, Dioscorides, in 70 AD, wrote *Materia Medica*, which discussed cannabis as a material to make strong rope and as treatment of ear aches as well as decreased libido (4). This publication was an influential medical treatise for the next 1500 years. Galen (129–200 AD), another Greek who was a physician to the Romans, commented on a pot-seed dessert

consumed by Romans and noted that an overdose of this substance could "affect the head by sending to it a warm and toxic vapor" (4).

Cannabis became a popular product in the Middle East in the 12th century and thereafter spread to other parts of the world (15). Li Shi Chen (1517–1593) became a medical textbook writer in China and rewrote as well as updated classic Chinese medical texts; in his "The Great Herbal of Medicine" he includes use of medical cannabis (9). Indeed, the use of medicinal cannabis may date back to ancient China, as far back as 4,000 BCE (9). The French and British cultivated cannabis in early America in Virginia and Plymouth in 1632 (16).

Of course, other drugs have emerged in the modern world with roots to the ancient. For example, ancient and native South American Indians were pleasured by the mild stimulant effects of chewing coca leaves from the plant *Erythroxylon coca*. This stimulant pleasure is similar to that of caffeine, which is utilized by billions of people in the 21st century. Life would have been safer if humans remained at an abecedarian knowledge of coca and simply chewed it. However, science complicated this issue. Albert Niemann (1834–1861), a PhD student, was given imported coca leaves by his supervisor (Dr. Friedrich Wöhler, 1800–1882) at the University of Göttingen in Germany with a request to study it. The obedient Niemann, in 1859, then was able to isolate an alkaloid he called *cocaine* and dutifully published his results in 1860 (17). His work of noesis earned him his doctoral degree, but his premature death in 1861 at age 27 prevented Dr. Niemann from seeing the death and carnage this extreme drug of euphoria would cause for countless millions of humans in the world of the 19th, 20th, and now 21st century (18).

Another deadly plant, tobacco, was first consumed by pre-Columbian American natives. These American Indians grew tobacco and developed ceremonial as well as medical uses for smoking this Trojan-horse product. It was introduced to Europe in the 16th century and was popularized by such figures as the French diplomat Jean Nicot, for whom nicotine was named. Use of tobacco was increased after the U.S. Civil War (1861–1865) by the overwhelming amount of tobacco grown in North Carolina and Virginia. Cyclopean and predatory promotion by the tobacco corporations and the movie industry increased the use of tobacco in the 20th century until the historic release of the first report of the Surgeon General's Advisory Committee on Smoking and Health on January 11, 1964. This report by Luther L Terry, MD, identified the severe adverse effects of tobacco as a tenebrous product that first addicts the victim and later kills him or her with cancer or heart disease (19). The U.S. government has launched a major, ongoing campaign since then to educate the unwary public to the major dangers of tobacco, resulting in far fewer Americans addicted to tobacco in the 21st century in contrast to the previous century (20).

Despite current knowledge of the minacious nature of tobacco, the premature deaths of over 400,000 Americans each year from tobacco (5 million worldwide), the publicized prestidigitation of tobacco apologists, and the widespread global

medical philippics on *Nicotiana tabacum*, this Plutonian product continues to be grown and promoted with the aid of governments, societies, and the truculent tobacco enterprise. In its 31st publication on tobacco by the U.S. Surgeon General's office, the government concludes that the threat on the health of youth and young adults remains real and unremitting (20). Indeed this plant turns our youth and young adults into helpless myrmidons who blindly smoke this chemical until they prematurely die years later from its relentless and well-known complications. In order to replace these large numbers of tabescent and dead people, younger humans are tragically and lubriciously targeted for tobacco addiction by a powerful, brummagem industry.

Thousands of years of searching for the perfect chemical to produce joie de vivre has resulted in many drugs of addiction that are available to humans. Just as cannabis is currently idolized by media stars and others as a condign chemical to enhance life, cocaine was at first praised as an ideal chemical to assist in amelioration of life's woes. For example, the well-known 19th-century English detective Sherlock Holmes was a classic cocaine addict, as fictionalized by the famous Scottish author and physician Sir Arthur Conan Doyle (1859–1930).

One could speculate that cocaine lead to sweeping changes in mental health management. An Austrian neurologist, Sigmund Freud (1859–1930), was an advocate of cocaine utilization to promote happiness, sexual pleasure, and health; indeed, he wrote a landmark, thrasonical paper of praise for cocaine in 1884 (21). However, sensible science began to arise with a published critique of Freud's praise of cocaine by Albert Erlenmeyer who criticized Freud's use of cocaine to treat morphine addiction and initiated the understanding of cocaine's adverse effects (22). Freud left his hometown of Vienna to escape this barrage of embarrassing criticism and reinvented his career in Paris as the father of psychoanalysis. Freud no longer advocated for the "wonders" of cocaine.

Another "wonder" drug, heroin, has also played a major yet treacherous role in the history of the world (18,23). Analgesic effects from chewing or swallowing Opium poppy seeds (*Papaver somniferum*) was written about in both Egyptian and Roman texts of the past centuries. However, it was not until 1806 that a German pharmacist's assistant, Friedrich Wilhelm Adam Sertürner (1783–1841), identified morphine in attempts to chemically find the part of opium that induced sopor. It was called *morphine* after Morpheus, the Greek god of dreams, and Sertürner spent many years studying the effects of this sleep-inducing agent on himself and others. Reliable syringes were developed in Edinburgh in 1853 and the intravenous delivery of these drugs has exploded ever since. Control of opium became part of the 19th-century Opium Wars between the Qing Dynasty in China and the British as well as the French empires from 1839 to 1842, and then the United States from 1856 to 1859 (24).

Much like cocaine, the use of morphine was touted as a cure for various conditions until the true minacious effects of addiction were realized. Morphine was liberally used for injured soldiers in the U.S. Civil War and wounded veterans were sent

home with morphine and hypodermic needles. A London chemist, C.R. Alder Wright, identified diacetyl-morphine in 1874 as he sought a nonaddictive derivation of morphine. A chemist at the Bayer laboratories, Heinrich Dreser, found that Wright's discovery had remarkable analgesic properties and also appeared to improve pulmonary problems. Bayer then marketed it in 1898 as a sedative, anti-tussive medication and named diacetyl-morphine with the term *heroin* for its "heroic" property of analgesia. Bayer stopped heroin production in 1913 due to its addictive, precarious potential and focused on his other product – aspirin.

There were an estimated one-quarter of a million morphine/heroin addicts in the United States in the early 1900s. Addictive chemicals such as morphine and cocaine were unregulated and available without prescription from physicians as well as from drugstores, traveling salesmen, and even via the mail. Dr. William Halsted (1850–1922), notable John Hopkins surgeon and contemporary of Freud, started his cocaine addiction as he introduced regional anesthesia with this compound. Years later, he was to exchange the use of cocaine for morphine (25).

As the major problem of drug addiction was slowly realized, legal measures against drugs were gradually developed in the United States. Opium establishments (so-called dens) were outlawed in San Francisco in 1875, but the first national drug law was not established until 1906 with the Pure Food and Drug Act, which ordered accurate labeling of patent chemicals that contained various drugs and started regulation for such drugs as alcohol, opiates, cocaine, and cannabis.

Finally, in 1914, critical doses of opiates and cocaine were restricted to licensed physicians and pharmacies; this law was called the Harrison Narcotic Act. At this time heroin was fully banned and physicians were not allowed to legally prescribe narcotics even as part of a maintenance program for addicts. Alcohol came under regulation as well, even though this chemical had been well-known for thousands of years and mentioned in various biblical texts. The United States officially prohibited alcohol in 1919 (through the Eighteenth Amendment to the U.S. Constitution), but prohibition of alcohol was eventually repealed in 1933. Cannabis was well accepted in the United States for a time and was even grown by the leading forefathers of the country. However, the battle against cannabis intensified with the 1937 Marijuana Tax Act, which made it illegal to buy, sell, barter, or give away cannabis in the United States.

The 20th century also saw the rise of methamphetamine, a drug first synthesized as amphetamine in 1887 in Berlin, Germany, by Romanian chemist Lazar Edeleanu. Methamphetamine was developed from ephedrine by a Japanese chemist, Nagai Nagayoshi, in 1893; crystallized methamphetamine was synthesized by pharmacologist Akira Ogata in Japan in 1919 (26). Ephedrine had been isolated from the plant Ma-Huang (Ephedra) in 1887 by Nagayoshi Nagai. As with other now illicit drugs, methamphetamine was first hailed as a wonder drug and was used to treat narcolepsy, keep World War II fighter pilots awake, manage obesity as well as attention-deficit hyperactivity disorder, and even help assuage heroin addiction in the 20th century

(27). However, as with other devious and duplicitous drugs of addiction, its adverse effects were gradually recognized and it was identified as a controlled drug in the United States in the 1970s. Its fame has spread among the world of addiction and rural labs making this chemical (from ephedrine, pseudoephedrine, and anhydrous ammonia) have sprung up all over the United States since the 1990s.

The 20th century was characterized by each subsequent decade having an ebb and flow in drug addiction as well as marked by a fear that comprehensive drug education in children and youth would augment drug addiction. There was a dithyrambic explosion of drug use in the 1960s based on the so-called hippy and free-love generation. Cannabis remained a popular drug and the battle to make cannabis legal has been waged ever since with the a fortiori, accipitrine argument that marajuana is safe and good for the public to use. This vade mecum considers this eristic argument and other issues in the vast and complex phenomenon of substance abuse in adolescents and young adults.

Wars for control of drugs of addiction continue in the 21st century as war lords ruthlessly fight to gain the rewards of fortune in the multibillion-dollar drug trade. We have learned that drug addicts have a saturnine brain disorder that makes them seek their drugs of choice at any price even if this price leads to lifelong addiction, imprisonment, hospitalizations, poverty, high morbidity, and premature death (28–32). We have also learned that drugs of addiction and euphoria are numerous and even include medications that are prescribed by clinicians (33). We know about the link of substance experimentation and abuse with overall high-risk behavior in adolescents and young adults (34). We have learned that simply relying on abstinence-only education ("Just Say No!") and punishment with incarceration for drug use does not reduce or ameliorate the drug use and abuse epidemic in the world (35). Links between substance-use prevention and its impact on mental health treatment remain to be elucidated (36).

Drug addicts have rapacious needs that are often never satisfied. Youth must learn that drug dealers do not conduct an ecumenical, eidolonic, eleemosynary business but are esurient epigones and panjandrumic, Pecksniffian, peculating pied pipers often falsely and tragically idolized by the eristic media.

Thus, we desperately need guidance in learning how to prevent drug addiction in our youth and establish prevention programs to decrease the devastating toll it has and will take on billions of human beings in this century and beyond (37–39). We must be concerned about drug addiction and its tenebrous effect on our youth, including their alarming use of nonmedical analgesics (40). It is important to study youth in their communities and thus support more community-based research protocols (41). It is useful to know what is salubrious in substance abuse management as well as what is not salutary (42,43). We must not remain desipiently pococurante with respect to the Faustian dangers of drug addiction for our youth.

This effusive enchiridion on substance abuse in adolescents and young adults provides au courant information on this global, brobdingnagian, bunyanesque topic. We cover a wide variety of subjects within the paradigm of drug abuse and agree with the 21st-century message of integrating substance abuse management with primary care services (44). The editors thank the many experts who so graciously and lambently provided their time and knowledge in these areas. The editors hope that the readers of this treatise find useful and beneficial information that will help them in their work seeking to understand and ameliorate the negative effects of these plants of paradise and of other chemicals that are part of the drug addiction pharmacopoeia of the 21st century (45). We must not be seen as being fainéant with regard to helping our apolaustic youth in their agons with addictive chemicals. We must rescue our adolescents and young adults from their stygian journey of drug addiction and return them to a prelapsarian, supernal existence devoid of these caustic chemicals. There is simply nothing more important that adults of this world should do for their children. The Zeitgeist of the 21st century should be a spirit of true love for our youth marked by a renewed willingness to help our adolescents and young adults avoid a lifetime of maundering addiction.

I would rather have a life span of ten years with coca than one of ten million centuries without it.

– Paolo Mantegazza (1831–1910), Italian physiologist and neurologist (16)

References

1. McHenry HM. Human evolution. In: Ruse M, Travis J, eds. Evolution: The first four billion years. Cambridge, MA: Belknap Press, Harvard University Press, 2009:265.
2. Houston SD. The first writing: Script invention as history and process. Cambridge, MA: Cambridge University Press, 2004.
3. Milestones in the history of marijuana. Accessed 2012 Dec 01. URL: http://brainz.org/420-milestones-history-marijuana/
4. Abel EL. Marijuana. The first twelve thousand years. Accessed 2012 Dec 01. URL: http://druglibrary.org/schaffer/hemp/history/first12000/abel.thm
5. Grollman AP. Alternative medicine: the importance of evidence in medicine and medical evidence. Is there wheat among the chaff? Acad Med 2001;76(3):221–3.
6. Yearbook of the United States Department of Agriculture 1913;288.
7. Belda A, Peiró V, Seva E. The relationship between plants used to sustain finches (Fringillidae) and uses for human medicine in southeast Spain. Evid Based Complement Altern Med 2012; 2012:360913.
8. Rawlinson G. The Histories. Herodotus of Halicarnassus. 430 BC. Translated in 1858. Accessed 2012 Dec 01. URL: http://classics.mit.edu/Herodotus/history.html
9. Medical cannabis. A short graphical history of China. Accessed 2012 Dec 01. URL: http://antiquecannabisbook.com/chap2B/China/China.htm
10. Scholl R. Der Papyrus Ebers. Die grösste Buchrolle zur Heilkunde Altägyptens (Schriften aus der Universitätsbibliothek 7). Leipzig, Germany: Universitat von Leipzig, 2002. [German]

11. Greydanus DE, Patel DR, Feucht C, eds. Preface: Pediatric and adolescent psychopharmacology. Pediatric Clin North Am 2011;58(1):iii–iv.
12. Eddy NB. The history of development of narcotics. Law Contemp Prob 1957;22(1):22–5.
13. Greydanus DE, Feucht C. Performance-enhancing drugs and supplements. In: Patel DR, Greydanus DE, Baker RJ, eds. Pediatric practice: Sports medicine. New York, NY: McGraw Hill Medical. 2009:63–77.
14. History of beer. Accessed 2012 Dec 01. URL: http://en.wikipedia.org/wiki/history_of_beer
15. Escohotada A. A brief history of drugs. London: Park Street Press. 1999.
16. Courtwright DT. Forces of habit. Cambridge, MA: Harvard University Press. 2001.
17. Niemann A. Ueber eine neue organische Base in den Cocablättern. Archiv der Pharmazie 1860;153(2):129–256. [German]
18. Greydanus DE, Patel DR. The adolescent and substance abuse: Current concepts. Disease-a-Month 2005;51(7):387–432.
19. United States. Surgeon General's Advisory Committee on Smoking and Health United States. Rockville, MD: Public Health Service, Office Surgeon General Luther Terry Surgeon General Report, 1964.
20. Preventing tobacco use among youth and youth adults. A report of the Surgeon General. Rockville, MD: US Department Health Human Services, Public Health Office, Office of the Surgeon General, 2012.
21. Freud S. Über Coca. Centralblatt für die ges Therapie 1884;2:289–314. [German]
22. Koelbing HM. Cocaine addiction 100 years ago. A. Erlenmeyer: Uber cocainsucht. [Deutsch] Medizinal Zeitung 31 Mai 1886. Schweiz Rundsch Med Prax 1986;75:1565–8.
23. Accessed 2012 Dec 01. URL: www.narconon.org/drug-information/heroin-history.html
24. Waley A. The opium war through Chinese eyes. London: Allen Unwin, 1958; Reprinted Stanford, CA: Stanford University Press, 1968.
25. Toledo-Pereyra LH: Vignettes on surgery, history and the humanities. Austin, Texas: Landes Bioscience, 2005.
26. Accessed 2012 Dec 01. URL: http://en.wikipedia.org/wiki/Methamphetamine
27. Greydanus DE, Pratt HD. Attention-deficit/hyperactivity disorder in children and adolescents: interventions for a complex costly clinical conundrum. Pediatr Clin North Am 2003;50:1049–92.
28. Hanion CA, Canterberry M. The use of brain imaging to elucidate neural circuit changes in cocaine addiction. Subst Abuse Rehabil 2012;3(1):115–28.
29. de Los Rios F, Kleindorfer DO, Khoury J, Broderick JP, Moomaw CJ, Adeove O, et al. Trends in substance abuse preceding stroke among young adults: a population-based study. Stroke 2012; 43(12):3179–83.
30. Jouanjus E, Pourcel J, Saivin S, Molinier L, Lapeyre-Mestre M. Use of multiple sources and capture-recapture method to estimate the frequency of hospitalizations related to drug abuse. Pharmacoepidemiol Drug Saf 2012 May 02. doi: 10.1002/pds.3280.
31. Beletsky L, Rich JD, Walley AY. Prevention of fatal opioid overdose. JAMA 2012;308(18):1863–4.
32. Alexander GC, Kruszewski SP, Webster DW. Rethinking opioid prescribing to protect patient safety and public health. JAMA 2012;308(18):1865–6.
33. Currie CL, Wild TC. Adolescent use of prescription drugs to get high in Canada. Can J Psychiatry 2012;57(12):745–51.
34. McGuire J, Want B, Zhang L. Substance use and sexual risk behaviors among Mississippi public high school students. J Miss State Med Assoc 2012;53(10):323–8.
35. Brown JH, Clarey AM. The social psychology of disintegrative shaming in education. J Drug Educ 2012;42(2):229–53.
36. Salvo N, Bennett K, Cheung A, Chen Y, Rice M, Rush B, et al. Prevention of substance use in children/adolescents with mental disorders: a systematic review. J Can Acad Child Adolesc Psychiatry 2012; 21(4):245–252.

37. Kuehn BM. WHO documents worldwide need for better drug abuse treatment – and access to it. JAMA 2012;308(5):442–3.
38. Greydanus DE, Feucht C, Patel DR. Pharmacologic management of substance abuse disorders in adolescents: current concepts. In: Merrick J, ed. Child and adolescent health yearbook. New York: Nova Science, 2010:297–309.
39. Greydanus DE. Drug addiction and our youth. Int J Child Adolesc Health 2011;4(3):211–2.
40. Miech R, Bohnert A, Heard K, Boardman J. Increasing use of nonmedical analgesics among younger cohorts in the United States: a birth cohort effect. J Adolesc Health 2013;52(1):25–41.
41. Vaughn LM, Wagner E, Jacquez F. A review of community-based participatory research in child health. MCN Am J Matern Child Nurs 2013;38(1): 48–53.
42. Peloquin SM, Ciro CA. Self-development groups among women in recovery: client perceptions of satisfaction and engagement. Am J Occup Ther 2013; 67(1): 82–90.
43. Rucklidge JJ, Kaplan BJ. Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review. Expert Rev Neurother 2013;13(1):49–73.
44. Padwa H, Urada D, Antonini VP, Ober A, Crèvecoeur-MacPhail DA, Rawson RA. Integrating substance use disorder services with primary care: the experience in California. J Psychoactive Drugs 2012; 44(4):299–306.
45. Greydanus DE, Feucht C, Hawver EK. Substance abuse disorders. In: Greydanus DE, Patel DR, Omar HA, Feucht C, Merrick J, eds. Adolescent medicine: Pharmacotherapeutics in general, mental, and sexual health. Berlin: De Gruyter, 2012:157–99.

Section I: **Etiology and diagnosis**

2 Neurobiology of substance use disorders

Ahsan Nazeer and Michael R. Liepman

Substance use disorders pose a significant burden to communities and societies across the world. Primarily disorders with onset in childhood or adolescence, untreated substance use disorders typically progress into adulthood, growing in severity and becoming chronic, relapsing, and potentially fatal disorders. Resulting morbidities and sometimes mortality cause a staggering amount of medical and societal costs. Understanding the causes of addiction and underlying neurobiological processes is an active area of research. Most of the current knowledge is derived from preclinical studies and animal models of addiction. The following is a brief review of the mechanisms underlying the addiction process.

2.1 Introduction

Substance use disorders are characterized by a chronic remitting and relapsing course. Symptoms of tolerance and withdrawal are characteristics of physical dependence, but maladaptive patterns of behavior are key to the diagnosis of substance use disorders. In this chapter we briefly review the neurobiology of addictive disorders and for the sake of simplicity, the previously mentioned terms will be used interchangeably. Psychoactive substances act on the neuronal structures and processes that are important for the regulation of healthy mood, behavior, and motivation. Most of the current understanding of this cause and effect is derived from animal models of addiction. These models have been particularly helpful to demystify mechanisms at the neuronal and synaptic level during the acute phase of drug intake. With advancement in research techniques, animal models of chronic drug preference, self-administration, reward, cravings, tolerance development, and withdrawal are being developed in order to better understand the neuroadaptive mechanisms underlying long-term use. Use of genetic variants and characterization of receptor subtypes and interacting neuronal circuits have advanced our understanding of how addictive drugs work in the brain. More recently, the use of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided critical insights into this highly complex neurocognitive loop. Progress in neurobiology is so rapid that we can only hope to capture a snapshot of today's view because what we know keeps changing.

2.2 General concepts

In the majority of cases, substance use starts either as a recreational activity or as a means to gain some perceived benefits from a particular drug (e.g., pain relief from prescription opioids, control of anxiety, anger, depression, or increasing energy or

attention). With repeated intake, a maladaptive pattern of use and loss of control of consumption accompanies the transition to drug dependence. Seeking faster routes of administration, escalating doses, evolution of purpose for taking the drug, repetitive patterns of use, shifting social support networks to incorporate mostly other users, ease of access to drugs, abandoning healthy supports and activities, emotional stress, disregard of danger warnings, and lack of enforcement of safety procedures all play roles in facilitating the progression to harmful addictive use. At this stage, the individual's use becomes more habitual and continues despite ongoing adverse effects and deterioration in psychosocial functioning. From a clinical point of view, this use results in the emergence of complex behavioral problems that probably are a result of substance-induced neurochemical changes in the nervous system.

During the early days of addiction research, the brain reward system was considered the final common pathway in the addiction process. Recent research, however, has shown that the addiction models are more complex than can be explained by the reward model alone. In addition, it is important to understand that the effects of drugs on the reward system continue to play an important role in the overall understanding of the neurobiology of addiction (1). Numerous brain structures are involved in the circuitry of learning, motivation, reward, and pleasure. The caudate, putamen, globus pallidus, and amygdala constitute the basal ganglia. The caudate and putamen together are called the striatum. The nucleus accumbens (NAc) is associated with reward, motivation, and learning. The hippocampus in the limbic system has widely dispersed neuronal connections and plays a role in the development of dependence. Other areas of interest include: orbitofrontal cortex (inhibitory control), prefrontal cortex (executive control), and hypothalamic-pituitary-adrenal axis (associated with stress).

Given the importance of these areas in the regulation of behavior and emotion, it is no surprise that these structures have been the focus of intense scrutiny in substance abuse research. Particularly, dense connections between these areas and the forebrain, including mesolimbic and mesocortical DArgic pathways, have been considered central to the positive reinforcing effects of drugs. Although many consider that understanding how these areas interact with each other and the neurotransmitters involved are key to understanding the addiction model, the realities are quite complex. With ongoing research, the role of non-DArgic systems and deficits in the frontal cortex also are coming to the forefront.

Our understanding of personal genetics has revealed numerous mutations in genes for various structures in the brain, including receptors, transporters, and enzymes. Epigenetic processes also become involved with chronic exposure to high doses of drugs. Complex interactions between neurons modulate presynaptic and postsynaptic activities. Heavy repetitive exposures to certain drugs may generate signals to cell bodies to increase populations of receptors affecting levels of tolerance.

2.2.1 Dopamine

Dopamine (DA) was discovered by Nobel laureate Arvid Carlsson. DA, along with serotonin and epinephrine, is one of the most widely studied and researched neurotransmitters in the nervous system. It is involved in numerous key functions, including the regulation of fine motor movements, learning, motivation, and cognitive functioning. Numerous stimuli including food, sex, and addictive drugs increase intrasynaptic DA levels in the nucleus accumbens (NAc) via their effects on the ventral tegmental area (VTA) (2). It is now known that the NAc responds to the motivational aspect of the stimuli while the striatum is associated with behavioral execution. DA plays a vital role in this mechanism and the DA reward pathway has been the center of addiction research for several decades (3). However, it is worth noting that the underlying neurobiological mechanisms of reward and pleasure are especially complex, and DA does not appear to be the sole culprit in this pathway. It is noted from the fact that numerous noxious and novel stimuli can increase DA within the NAc without causing a reward or an addiction potential.

Acute DA release in the NAc also does not fully explain the desire and compulsions that arise when individuals are exposed to places, persons, and paraphernalia of drug use (triggers, cues). Other evidence comes from animal models with a hypoDArgic genetic trait who, despite the DA signal blockage, continue to show pleasurable responses to sweet fluids (4). Another observation against DA being the sole neurotransmitter in addiction came from the observation that opiates, ethanol, nicotine, and cannabis appear to bypass the DArgic system while still maintaining part of their addiction potential.

It is worth noting that animal models of addiction have shown a variable pattern of DA neuronal firing that is as much dependent on cues to reward as to the reward itself. In these models, a reward causes firing in DA neurons, but as the animals learn the signals, response to reward habituates and firing occurs in response to the cues themselves (5–6). This pattern suggests extensive input from the cerebral cortex and interactions between the hippocampus, amygdale, and striatum, implicating complex pathways in this neurocircuitry of reward, craving, and habituation. With repeated stimuli, a homeostatic state is reached that is indicated by decreased DA response to such stimuli, a condition synonymous with tolerance in humans.

Numerous studies also have converged on the hypothesis that the previously mentioned cue-based neuronal firing is the cause of persistent drug use. This hypothesis is supported by the fact that most drug use and relapses follow exposure to environmental cues, including places of drug use, drug-using peers, and drug-related paraphernalia. These processes gradually lead to long-term changes and reorganization of neuronal circuitry. The candidate mechanisms underlying this neuronal

reorganization are long-term potentiation (LTP) and long-term depression (LTD), the same processes that are also involved in long-term memory and learning.

So far, five DA receptors have been identified and are categorized into two different families.

2.2.1.1 D1, D5 receptors

These receptors are G-protein linked and stimulate cyclic AMP (adenosine monophosphate). They are located postsynaptically and are associated with reward and behavioral inhibition (7). Stimulants, cocaine, ethanol, and food stimulate D1 receptors. This activation causes numerous extra- and intracellular changes including induction of Fos in the NAc and caudate-putamen regions. Research is ongoing to identify the exact role of D1 receptors in the addiction process. In preclinical studies, an increased pattern of cocaine self-administration is found among animals that were exposed to a DA antagonist (8). This behavioral change can be explained by super-sensitivity of DA receptors in the NAc, an observation that suggests a role of D1 receptors in the addiction process.

2.2.1.2 D2, D3 receptors

These receptors also play a major role in the signaling of DA neurons. Studies using animal models have yielded complex results. Pharmacological blockade of D2 receptors leads to decreased response to morphine and ethanol (9). D2 receptors have two isoforms: D2L, which has postsynaptic effects, and D2S, which acts as presynaptic autoreceptor. Because of its inhibitory function as presynaptic autoreceptor, in genetically modified D2-negative mice administration of cocaine causes significant elevations in the striatum (10). positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies have shown decreased D2 density in frequent users of cocaine, heroin, and methamphetamine (11). Other studies have found an inverse correlation between the D2 receptor density and self-administration of cocaine (12). In human studies of ethanol and methylphenidate, individuals with fewer D2 receptors were found to require higher doses of these drugs in order to get the same response in comparison to individuals with higher D2 density in the NAc (13). Whether the decrease in D2 receptors is a predisposing event that causes drug addiction, is an area of ongoing research (14).

D3 receptors are mainly localized in the limbic region and are structurally similar to D2 receptors. In animal studies, pharmacological blockage of these receptors was found to reduce ethanol-seeking behavior, self-administration of ethanol, and reinstatement of cocaine- as well as nicotine-seeking behaviors (15–17).