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Stimulant Abuse: Pharmacology, Cocaine, Methamphetamine, Treatment, Attempts at Pharmacotherapy

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Keywords

Stimulants; cocaine; amphetamine; methamphetamine

Stimulant use and abuse: a primary care issue

Recent history

Stimulants, including cocaine and amphetamines, are among the most widely used and abused illegal substances in the United States. Coca chewing has a long history of indigenous use in South America 1. Widespread use of cocaine followed its isolation from coca in 1859 and a medical publication purporting its benefits in 1884. Its subsequent incorporation into patent medicines and popular beverages, e.g., Vin Mariani and Coca-Cola contributed to its profligate use [2]. Rising social and medical problems raised concern in many circles and restrictions were gradually applied until the Harrison Act (1914) banned all OTC inclusion of cocaine [3]. In the US, a popularity wave of cocaine began in the 1970's followed by the crack wave of the 1980's 4. These waves have left paths of adverse consequences, including association with the HIV epidemic, in the latter decades of the 20th century.

The first of the synthetic stimulants, amphetamine (isolated in 1887), was first popularized in the 1930's with an OTC nasal decongestant (Bezedrine inhaler) containing the amphetamine phenylisopropylamine and the following the discoveries of clinical applications for fatigue, narcolepsy and depression [5]. High availability, and popularity, led to misuse and OTC use was banned in 1957. Prescription misuse followed WWII (with common military usage) and illicit diversion of medications. Methamphetamine (isolated in 1919) use peaked during the late 1960's creating a "speed scene." The passage of the Controlled Substances Act in 1971 led to a dramatic decline in prescribed amphetamine and the popularity of amphetamines and methamphetamine declined for a time 6. The 1990's brought a reemergence of methamphetamine, particularly to the western US, concurrent to mounting small scale production, aka "meth labs," first in California and subsequently spreading nationwide 7. New forms of methamphetamine, e.g., "crank" and "ice," have had

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their popularity waves as well. The popularity of amphetamines is reciprocal with cultural representations throughout the 1940's – 1990's, e.g., in literature, movies and music 8, 9.

Epidemiology

According to the National Survey on Drug Use and Health (NSDUH), the national prevalence of current cocaine use is third after marijuana and misuse of prescription medications. The estimated lifetime prevalence of cocaine use is 14.7% of the US population 12 years of age or older (3.4%, crack use prevalence). Current use (past month) of cocaine was reported by 0.7% of persons aged 12 and older in 2008, decreasing significantly from 1.0% in 2003. The proportion reporting current crack use, 0.1%, also decreased from 2003 levels (0.3%) [10]. The NSDUH may underreport drug use in certain populations, including the homeless, institutionalized persons and college students.

The estimated lifetime prevalence of non-medical amphetamine use is 8.5% of the US population according to the NSDUH 2008, down from 9.7% in 2003. Current use of all amphetamines is reported at 0.4% (2008) down from 0.6% (2003); only 0.1% of the population reports current methamphetamine use in the latest survey; this is decreased from 0.3%. Methamphetamine use is more prevalent in the western US, but is trending eastward [11].

The Drug Abuse Warning Network (DAWN) is a national survey of non-federal short-stay hospitals with 24 hour emergency departments (ED) of patient visits associated with drug misuse or abuse; DAWN has a separate survey of medical examiner data on mortality related to illegal drug use. According to the 2006 DAWN survey, one in three (31%) of all drug-related emergency visits involved cocaine; methamphetamine was associated with 5% of all ED visits and amphetamine, 2%. No statistically significant change in stimulant-related ED mentions was noted over the past two annual surveys [12]. In the DAWN mortality state profiles, cocaine was one of the top 3 drugs involved in drug-related deaths in six of ten states; stimulants (amphetamines and methamphetamine) ranked in the top 10, of mortality involved drugs, in six of ten states; with four being western states 13. While household surveys report low methamphetamine use prevalence, regional law enforcement agencies are reporting heightened concerns. In addition, the associated economic and societal costs of methamphetamine use are estimated to be high 14.

Forms, preparation and use

Cocaine

Cocaine is a naturally occurring alkaloid in the leaves of the coca plant, *Erythroxylon coca*, which is indigenous to the Andean region of South America. The area of coca under cultivation in Colombia, Peru and Bolivia peaked in 2000 at 221,300 hectares, subsequently declining to 167,600 hectares in 2008. Most of the cocaine derived from this harvest is for export. Estimates of potential cocaine production for the region have varied little since 1994: in that year estimated production was 891 metric tons; since peaking in 2000 at 1008 metric tons there has been a decline to 845 metric tons in 2008. Global cocaine seizures have risen dramatically in the last decade: in 2007, 711 metric tons of street-level cocaine were seized, double the amount in 2000. Adjusting for purity, an estimated 42% of global pure cocaine was reportedly confiscated in 2007 [15].

Cocaine is street-available in both acidic (salt) and basic forms 16. Cocaine hydrochloride (aka, "coke," "blow," "snow," "nose candy," "yayo") 17 is a water soluble powder with a high melting point. As such it is bioavailable (~30–60%) through insufflation (i.e., snorting, or "tooting"), or easily dissolved for intravenous injection; it is not usually smoked as the active ingredient is destroyed by the temperatures required for vaporization. Time to peak

subjective effect averages 14.6 minutes after insufflation compared to 3.1 minutes following injection 18. Nasal absorption is limited due to the vasoconstrictive properties of cocaine.

Base cocaine, aka "crack," or "rock" 17, can be vaporized and inhaled due it is lower melting point. The term "crack" reportedly comes from the sound the material makes while melting [6]. Since its entry into the US market in 1985, crack cocaine rapidly spread due to its low cost and rapid action. The time to reach peak subjective effect is significantly faster for smoked (1.4 min) than for intravenous or insufflated cocaine [18]. In the 1980's street-doses were frequently seen in US cities selling for as little as $2.50–5.00 19. Crack cocaine largely replaced an outmoded base form called "freebase," which involved a complicated series of dangerous steps to solubilize and extract base cocaine from its hydrochloride salt.

The average purity of cocaine available on US streets was 50–60% in 2007 [ref: DEA cocaine 2008]. Diluents, i.e., fillers, or "cut," include simple sugars, e.g., dextrose, starch, or white inert powders, e.g., talc. Adulterants, which may have some additive or mimicking active effects, include topical anesthetics, e.g., procaine, and cheaper stimulants, e.g., caffeine or ephedrine [20]. Reports of adverse consequences from levamisole (a veterinary medication) tainted cocaine have risen recently 21, 22. Cocaine is frequently used by heroin dependent users in combination, aka, "speedball." Tobacco, alcohol and marijuana are frequently used in conjunction with cocaine.

Amphetamine – methamphetamine

Historically, US illicit methamphetamine came from small producers in Mexico and California. The 1990's saw growth and spread in the domestic production of methamphetamine. DEA domestic methamphetamine seizures rose dramatically from 272 kilograms (kgs) in 1990 to 1,549 kgs in 2008 after peaking at 2,161 kgs in 2005 [23]. The number of US methamphetamine laboratory seizures increased from 7,025 in 2000 to 10,249 in 2003, declining to 2,584 in 2008 24. Much of this decline has been offset by increased importation of methamphetamine from Mexico. Methamphetamine can be made from OTC nasal decongestant products containing ephedrine and pseudoephedrine. For this reason, strict controls have been placed on OTC purchases and well as other precursor supplies. Since 2004, 44 states have restricted sales 25. Since 2005, the government of Mexico has progressively increased precursor controls with some measurable effect on production 24.

Methamphetamine exists in two stereoisomer, i.e., *l*- and *d*-, forms. *l*-methamphetamine has peripheral alpha-adrenergic activity and has been used in the past as a nasal decongestant (i.e., Vicks inhaler). *D*-methamphetamine (aka "speed," "crystal," "meth," or "crank") is a powerful stimulant with 3–5 times the CNS activity as the *l*-isomer and a half-life of 10–12 hours (cocaine's half life is 0.5–2 hours) [26]. It can be insufflated, smoked, injected, or inserted per rectum. Its forms are powder (usually white, but may be of other colors), or crystalline. "Ice" (aka "glass," or "Tina") is a highly purified form of *d*-methamphetamine which is intended for smoking; it vaporizes at an even lower temperature than crack cocaine [27, 28].

Amphetamines – other

Several synthetic stimulants, including amphetamine and methylphenidate, are available as prescription drugs. Forms include tablets, capsules, liquids and patches. Indications include attention deficit and hyperactivity disorder (ADHD), weight control and narcolepsy. OTC stimulants include aerosolized or ingested forms of decongestants as well as caffeine in multifarious forms [29]. There has been a recent boom of highly caffeinated beverages, aka, "energy" drinks 30.

Diversion of prescription stimulants is a concern. Given the increase in diagnosis of ADHD, the number of prescriptions for stimulant medication has grown. Surveys of college students reveal that illicit use of stimulants has grown recently and is at its highest level in decades [31]. However, there is no evidence that appropriate medical use of prescription stimulant medication leads to increased drug abuse. While studies examining cohorts of persons with ADHD confirm high prevalences of adult comorbid substance use disorders, they also find that treatment with stimulant medication is not associated with increased substance abuse in adulthood [32].

OTC stimulant-based appetitive suppressants have also raised concern over the past two decades. Fenfluramine-phentermine (aka Fen-phen) was a combination stimulant medication widely advertized and popular in the 1990's. Its adverse association with cardiac valvular regurgitation and pulmonary hypertension led to its removal from the market in 1997 [33]. An OTC decongestant and appetite suppressant, phenylpropanolamine, was removed from the market in 2005 after an association with hemorrhagic stroke among women was found 34.

Effects on Neurotransmitter Systems

Stimulants facilitate the activity of the monoamine neurotransmitters, i.e., dopamine, norepinephrine and serotonin, in the central (CNS) and peripheral nervous systems [35, 36]. Both cocaine and amphetamines act on presynaptic monoamine reuptake transporters, but each in unique ways. Cocaine is a reuptake inhibitor, i.e., it blocks the action of the reuptake transporter thus allowing more neurotransmitter to stay active in the synapse. Amphetamines are releasers, i.e., they are taken up by the transporter in exchange for neurotransmitter release into the synapse.

The reward circuit of the CNS includes dopamine pathways extending from the ventral tegmental area (VTA) of the midbrain to the pre-frontal cortex and limbic regions, including the shell of the nucleus accumbens and ventral pallidum; with the key areas for stimulant reward being the pre-frontal cortex and nucleus accumbens. Animal and human studies support the role of dopaminergic activity, particularly in these pathways, as mediating the behavioral effects of stimulants [36]. Cocaine and amphetamine intake transiently increases extracellular dopamine concentrations in the reward circuit 37. Affinity for the dopamine transporter is correlated to behavioral reinforcing effects in animal studies of varying stimulant potencies 38. Genetically engineered mice with dopamine transporters altered to not bind cocaine show no reinforcing affects of cocaine administration 39. Likewise, knockout mice lacking dopamine D_1 receptors do not self-administer cocaine 40. In human PET imaging studies, increases in dorsal striatum dopamine are associated with self-reported euphoric responses to acute stimulant use, as well as to conditioned drug cues 37. Blockade of more than half the dopamine transporters is required to reduce the psychological or behavioral effects of stimulants [41]. Thus, studies of dopamine receptor antagonists (e.g., antipsychotic medications) or synthesis inhibitors usually fail due to intolerance to the experimental drugs' effects [42].

Stimulants also increase serotonin and norepinephrine activity and have effects on a number of other neurotransmitter systems. Serotonin enhancement is contributory, but not obligatory, in the behavioral rewarding from stimulant use [43]. The subjective effects of stimulants of varying potencies are correlated with norepinephrine release [44]. Glutamate may play an important role in relapse to cocaine or amphetamine abuse [45]. Environmental cues and drug seeking leading to glutamatergic upregulation is a proposed model. Stimulants also increase acetylcholine release in the brain and may play a role in reward pathways [46].

Clinical features

Acute use: intoxication and overdose

The clinical effects of stimulant use, including psychological, behavioral and physiological effects, vary by acute versus chronic use, potency of drug, route of administration and dosage.

Acutely, use of stimulants leads to rapid neurotransmitter release resulting in euphoria, increased energy and libido, reduced fatigue and appetite, and behavioral responses, e.g., increased self-confidence and alertness [47]. Acute adrenergic effects include dose-responsive tachycardia and elevated blood pressure. Dose-equivalent responses to cocaine are seen with approximately 15–25 mg injected intravenously or smoked, 40–100 mg insufflated, or 100–200 mg ingested; oral amphetamine is approximately 10 times more potent per mg [48].

With escalating effective dose (i.e., by greater potency, amount or more efficient route) there is greater euphoria at first, but also increased likelihood of toxic and dysphoric effects including: insomnia, anxiety, irritability, confusion, paranoia, panic attacks and hallucinations; related behavioral consequences include impulsivity and grandiosity [49, 50]. Acute adrenergic side-effects include hyperpyrexia, hyperreflexia, tremor, diaphoresis, tachycardia, hypertension and tachypnea 51. Overdose may manifest in convulsions, cerebral hemorrhage or infarct, cardiac arrhythmias or ischemia, respiratory failure and muscle overactivity leading to rhabdomyolysis 52.

Chronic use

Chronic use of stimulants is frequently carried out in binge-abstinence cycles. Cycles of use can last 12 or so hours (typically cocaine) to several days (methamphetamine). This is reported in epidemiological studies [53, 54], as well as animal studies 55.

Cyclical use, drug craving and relapse may be explained by the concept of sensitization [56]. This occurs when intermittent use of a drug leads to enhanced effects; since the latter is often desired, cyclical use is learned and practiced. Repeated phasic use of low-dose cocaine may lead to increased sensitivity including startle reactions, repetitive and stereotyped behaviors, and alteration of motor function [57]. There is cross-sensitization among stimulants in that prior amphetamine administration subsequent boosts the effects of cocaine [58].

Some of the most prominent and disturbing effects of escalating stimulant use include a spectrum of psychotic features including, paranoia, delusions and hallucinations [59]. The latter include tactile hallucinations, or formication, colloquially referred to as “tweaking,” in which users will commonly pick at their skin, or perform other repetitive searching behaviors [60]. Twenty-five to fifty percent of chronic stimulant users report experiencing psychotic symptoms, and sensitization may worsen these with continued use [49, 61, 62]. Psychotic symptoms may also persist for years following abstinence from amphetamine use [63], with flashbacks reported by methamphetamine users up to 2 years following last use [64].

In time, neurotransmitter downregulation can occur, leading to an array of clinical features. Tolerance to the psychological and physical effects of stimulants may develop after several doses or within weeks [48, 65]. Imaging studies reveal decreased dopamine release and receptor availability in chronic users [37]. Changes in brain structure, e.g., decreased frontal cortex volume and enlarged basal ganglia, are also associated with chronic cocaine use [66]. Cognitive impairment may result and persist for months following abstinence [67].

Withdrawal from cocaine and amphetamine produces such a strong backlash of psychological and behavioral symptoms that it is frequently referred to as a “crash.” Acute

withdrawal symptoms include hypersomnolence, strong cravings and depression. Following this may be a several week period of dysphoria, lethargy and anhedonia [68, 69]. Relapses are common due to environmental cueing and the stark contrast between "high" and "crash" states.

Addiction

The potential for misuse, dependence and abuse of stimulants is high. Surveys of persons not in treatment estimate that 10–15% of stimulant users will become dependent 70; in treatment seeking populations the proportion exceeds 50% 71. Heavier use is clearly related to dependency, but route of use is also a key factor; stimulant smokers and injectors are more likely to become dependent [72]. Faster pharmacokinetics (e.g., smoked over ingested routes) and shorter peak to trough cycles (e.g., cocaine over methamphetamine) aid abuse potential [73].

The American Psychiatric Association Diagnostic and Statistical Manual (DSM-IV, Text Revision) requires several criteria be met for the diagnosis of stimulant abuse. The criteria include evidence of a maladaptive pattern of use, clinically significant impairment and more than one of the following (in a 12 month period): 1) failure to fulfill major role obligations; 2) use in physically hazardous situations; 3) recurrent legal problems; and 4) continued use despite social and interpersonal problems [74].

The variability seen individuals' responses to stimulants may be due to genetics, personality traits, or social/environmental cues (e.g., drug use setting), as well as a variety of other factors. The role of genetics is supported by twin studies, in which identical twins are highly concordant in the response to acute stimulant intake, initiation of stimulants and on stimulant dependence and abuse [75].

Medical complications

The medical consequences of stimulant abuse are many and occur in all major organ systems (Table 1). One way of understanding and categorizing these problems is by mechanism of injury, e.g., ischemia, nervous system stimulation, direct toxicity and other.

Mechanisms leading to tissue ischemia include vasoconstriction, vasospasm, endothelial damage and clotting stimulation (e.g., increased platelet activation and aggregation) 76. Stimulant use is associated with cerebrovascular disease and injury, including hemorrhagic and ischemic stroke 51; myocardial infarction (all aforementioned reasons plus increased oxygen demand) 77; renal failure (secondary to ischemia or rhabdomyolysis) 78, gastrointestinal disease (e.g., ulceration and intestinal infarction) 76, 79; muscle damage (also possible direct toxicity; leading to rhabdomyolysis, with up to one-third of patients developing acute renal failure) 76, 80; nasal and sinus damage 81; and reproductive complications (e.g., abruption placenta, low birth weight and feeding difficulties; concerns persist regarding infant cognitive deficits, but longer-term studies are somewhat reassuring) 82–84.

Excess nervous system stimulation secondary to stimulant use is associated with: seizures (usually tonic-clonic) 76, 85; movement disorders (increased basal ganglia dopaminergic activity resulting in repetitive behaviors, aka "tweaking," acute dystonic reactions, dyskinesia and akathisia, etc) 48, 86; and psychotic symptoms 63, 87 (both through dopaminergic excess 88 and focal perfusion deficits (methamphetamine) 89). Sympathetic nervous system stimulation leads to tachycardia and elevated blood pressure 51; endocrine stimulation or inhibition (e.g., dopamine inhibition of pituitary prolactin) 90; and sexual dysfunction 91.

Stimulant use may cause direct tissue toxicities resulting in associations with: cardiac arrhythmias (secondary to sodium channel blockade and increased norepinephrine) 92, 93; myocarditis and cardiomyopathy (toxic effect of drug or from chronic exposure to high levels of catecholamines) 92, 94; and pulmonary symptoms and disease (from acute shortness of breath to pulmonary edema; presumably due to combination of direct toxicity and vascular changes) 95, 96.

The pathophysiology of many of these adverse organ events is incompletely understood, and many have overlapping etiologies. In addition, some may be due to, or exacerbated by, drug contamination, or secondary to lifestyle (e.g., malnutrition) and social/environmental factors. A good example is “meth mouth,” dental and periodontal decay due to a combination of tissue shrinkage, poor fluid and high sugar intake, and neglect [97].

HIV

Use of stimulants is associated with HIV through drug and sexual risk taking, as well as though social mechanisms, e.g., poverty and sexual power dynamics. Drug injection is a well known risk with transmission increased by syringe/needle and paraphernalia sharing [98]. Cocaine use is associated with increased frequency of injection and needle sharing [99]. Injection risk behaviors also increase transmission risk for other viruses including HCV and HBV; HCV has a particularly high incidence among injection drug users [100].

Sexual risk (including risk taking and imposed social/power risk) is also increased among cocaine users with reported increased numbers of partners, increased frequency of unprotected intercourse, and exchange of sex for money or drugs [101]. Use of crack cocaine was independently associated with HIV in a large epidemiological study; transmission is likely through the confluence of poverty and sexual risk 102.

Use of methamphetamine is also associated with sexual risk taking leading to HIV and other sexually transmitted diseases (STDs) in both heterosexual and men-who-have-sex-with-men (MSM) populations [103]. Urban MSM have a much higher prevalence of methamphetamine use than that in the general population 104. In MSM cohort studies, methamphetamine use is associated with unprotected anal intercourse 105, 106. In a cross-sectional study of MSM, methamphetamine use concurrent with unprotected anal intercourse was an independent risk factor for recent HIV seroconversion 107. The use of erectile dysfunction (ED) medications, e.g., Viagra (sildenafil citrate), in the “party and play” scene is creating concern [103]. The combination of ED medication (or amyl/butyl nitrate, aka “poppers”) and methamphetamine is considered a sexual performance duo; the erectile dysfunction drug counters one of the common consequences of methamphetamine use 108. This combination unfortunately leads to increased sexual risk taking 109, STDs 110 and HIV seroconversion 111.

Treatment

Screening

In the primary care setting, substance use concerns lie in a continuum of risk and many patients with low- to moderate substance use disorders present sub-clinically. Screening for at-risk levels of alcohol use in the primary care setting has been given a B rating (recommended based on fair evidence) by the US Preventive Services Task Force (USPSTF) 112. However, according to the USPSTF, the benefit and clinical utility of screening asymptomatic patients for illicit substance use remains unclear 112. Other professional groups, e.g., American Academy of Pediatrics, recommend identification of adolescents at risk for substance use disorders 113 and the American College of Obstetrics and Gynecology recommends screening of pregnant women114. Many validated screening instruments exist, e.g., CAGE-AID (CAGE Adapted to Include Drugs), Alcohol Use

Disorders Identification Test (AUDIT; including adaptations for illicit drug screening) and Drug Abuse Screening Test (DAST). Given time and resource constraints, a consensus panel has recommended a single screening question: "Have you used street drugs more than five times in your life? [115]" Another single screening question has been recently tested for use in primary care settings (Dr. R. Saitz as cited in: Zgierska, 2009) 116: "How many times in the past year have you used an illegal drug or used a prescription medication for non-medical reasons?"

Screening, brief interventions and referral to treatment (SBIRT) is a clinical model with a growing evidence base. Brief intervention, focusing on risk reduction, involves client-centered counseling sessions assessing motivation to change, reflection on the personal consequences of drug use and setting of treatment goals. The Feedback, Responsibility, Advice, Menu of treatment options, Empathic and Self-Efficacy (FRAMES) model utilizing motivational interviewing is a key technique [117]. The evidence for the effectiveness of screening and brief interventions is extensive for reducing risky alcohol use 118–120 and evolving for addressing substance misuse. An evaluation of a large multisite Federally funded SBIRT service program found significant reductions in the proportion of patients using illicit drugs – including cocaine and methamphetamine – at 6-month follow-up 121. Additional studies support brief motivational intervention in reducing cocaine [122] and amphetamine use [123]. The adoption of 2008 Medicare and Medicaid billing codes should facilitate dissemination of SBIRT in primary care settings [116].

Behavioral/Social

Behavioral and psychosocial approaches are the mainstays of treatment for stimulant dependence, while pharmacological treatment remains elusive (see section below) [124]. These approaches include cognitive behavioral therapy, community reinforcement approach, contingency management, as well as combinations of these and other approaches. A meta-analysis of psychosocial treatments for cocaine abuse found a statistically borderline, but moderate reduction in combined dependency outcomes 125. Cognitive behavioral therapy focuses on learning strategies to change maladaptive patterns and increase coping skills; relapse prevention is a common goal. For cocaine dependence, use of cognitive behavioral therapy has been shown more effective than less intensive approaches 126–128, particularly for those with greater disease burden [129]. A recent review showed the effectiveness of cognitive behavioral therapy for the treatment of methamphetamine dependence [130].

Contingency management is one of the most promising approaches for the treatment of substance use disorders, including cocaine and methamphetamine abuse. The conceptual foundation of contingency management is based in operant conditioning; the study of how systematically applied conditions effect voluntary behavior. Artificially applied conditions are designed to either reinforce or punish a set of defined behaviors (e.g., drug use) to achieve a defined behavioral goal (e.g., drug abstinence) [131].

Contingency management falls on a spectrum of behavioral treatment options available in substance use treatment. Contingency management is unique in that it utilizes 'contrived' reinforcements to achieve the explicit goal of short-term drug abstinence. These reinforcements commonly include financial reward, or the use of vouchers for goods and services, e.g., housing. This differs from a community-reinforcement approach, which focuses on 'natural' social reinforcements that exist in the community, e.g., support from a social group or praise from a spouse.

The effectiveness of contingency management for substance use treatment is supported by a number of meta-analyses [125, 132–134]. For the treatment of cocaine dependence, effectiveness of contingency management has been shown in a meta-analysis [133] and several

randomized control trials [135–137]. Combining contingency management with cognitive behavioral therapy revealed no clear benefit from contingency management alone [135]. A community reinforcement approach combined with vouchers looks promising [138]. One persistent concern is that the effects of contingency management are short-lived, i.e., the benefits diminish once the vouchers are removed. In a study of contingency management versus cognitive behavioral therapy for stimulant dependence, contingency management was superior during the trial phase, but cognitive behavioral therapy was equivalent in effect once the trial was over [139]. Contingency management combined with cognitive behavioral therapy improved abstinence among methamphetamine users [140]. In a population of gay and bisexual men, contingency management improved methamphetamine use risk, while a culturally modified cognitive behavioral approach reduced sexual risk behavior [141]. A review of behavioral and psychosocial treatments for stimulant use found no evidence for difference in treatment efficacy between the management of cocaine and methamphetamine use [124].

Pharmacological

No medication is currently approved by the US Food and Drug Administration (FDA) for use in cocaine or amphetamine dependence. Numerous classes of medication have been studied, primarily in small clinical trials. Antidepressants, including heterocyclic, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and others have been explored and found to have no effect on cocaine abstinence [142]. A pooled analysis from a multisite trial of four medication classes, including antidepressants, mood stabilizers, dopamine agonists and neuroprotectives, found no significant effect on abstinence for any of the four classes 143. A combined approach of newer antidepressant medication and contingency management is showing promise 144, 145.

Summary

The high prevalence of use and harmful consequences makes screening, diagnosis and referral for treatment of persons with stimulant abuse a top concern for primary care providers. Having a working knowledge of use patterns, clinical symptomatology, end-organ effects and advances in treatment of stimulant abuse is essential.

While cocaine and amphetamine have different use patterns, duration of action, etc., the consequences of use are remarkably similar. Effective psychosocial treatments, e.g., contingency management, are available, while pharmaceutical treatment remains elusive. Primary care is at the forefront of screening, brief risk-reduction interventions and diagnosis of medical sequelae; with referral to addiction specialist treatment when necessary.

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Table 1

Medical complications of stimulant use

Organ system	Acute complications	Chronic complications
Central nervous system	Hallucinations, esp. tactile	Psychotic symptoms
	Dyskinesia	Cerebrovascular disease/stroke
	Seizures	Movement disorders, e.g., dystonic reactions, akathisia, choreoathetosis, tardive dyskinesia
Cardiovascular system	Tachycardia	Myocarditis
	Hypertension	Cardiomyopathy
	Myocardial infarction	Myocardial fibrosis
	Arrhythmias	Myocardial infarction
Pulmonary	Cough, shortness of breath, wheezing	Interstitial pneumonitis
	Pulmonary edema, hemorrhage	Bronchiolitis obliterans
	Pneumothorax	
Renal		Renal ischemia
		Renal failure
Gastrointestinal	Reduced gastric motility	Gastric ulceration and perforation
		Intestinal infarction
		Ischemic colitis
Liver		Viral hepatitis secondary to contaminated syringe use
Endocrine	Reduced prolactin	Inc, normal or dec. prolactin
	Increased epinephrine, CRH, ACTH, cortisol and luteinizing hormones	Normal testosterone, cortisol, LH, thyroid hormones
Musculoskeletal	Movement disorders (see CNS)	Rhabdomyolysis
Head and neck	Rhinitis	Rhinitis
		Perforated nasal septum
		Nasal and gingival ulceration
		Sinusitis
		Dental decay and periodontal disease
		Xerostomia
		Corneal ulcers
Immune system		Vasculitis sysndromes
Sexual function		Erectile dysfunction
		Irregular menses
Reproductive	Vaginal bleeding	FDA category C
	Abruption placenta	Placenta previa
	Premature rupture of membranes	Low birth weight
General/other	Dehydration	Weight loss
		Nutritional deficits