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Substance-Related Disorders in Adults

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Substance-related disorders are conditions in which an individual uses/abuses a substance, leading to maladaptive behaviors and symptoms. In Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition, text revision (DSM-IV-TR), substance-related disorders are further grouped into substance dependence and substance abuse.[1] Substance abuse refers to a maladaptive pattern of substance use leading to clinically significant impairment or distress, manifested by at least one symptom that interferes with life functioning within a 12-month period. Diagnostic criteria for substance dependence requires at least three of the following within a 12-month period: development of tolerance to the substance, withdrawal symptoms, persistent desire/unsuccessful attempts to stop the substance, ingestion of larger amounts of substance than was intended, diminished life functioning, and persistent substance use in the phase of physical or psychological problems. Substance abuse and substance dependence are enormous societal problems. In the United States, the lifetime prevalence of substance abuse or dependence in adults is over 15%. The cost of addictive illness in the U.S. is estimated to be over $144 billion annually in healthcare and job loss. Substance abuse prevalence is greatest among individuals 18 to 25 years of age. Substance abuse is also more common in men compared to women, and in urban residents compared to rural residents. An average of 20% of patients in general medical facilities and 35% in general psychiatric units present with substance abuse disorders.

Over 50% of individuals with substance-related disorders have comorbid psychiatric disorders. The term "dual diagnosis" usually refers to individuals with concomitant substance abuse and psychiatric diagnosis. Comorbid psychiatric diagnoses, common in individuals who abuse substances, include major depression, personality disorder, particularly antisocial personality, anxiety disorders, and dysthymia. Genetic studies

involving twins, adoptees, and siblings raised separately have suggested good evidence for familial patterns in alcohol abuse. Genetic patterns with other substances of abuse have not been well demonstrated.

Clinical Presentation

Substance abuse can manifest in a variety of formats dependent on substance used, pattern of use, and presence of comorbid illness. Commonly abused substances include alcohol, stimulant compounds (eg, cocaine and amphetamines), sedatives/hypnotic drugs (eg, barbiturates and benzodiazepines), opioids (eg, morphine, codeine), hallucinogens (eg, d-lysergic acid diethylamide/LSD), inhalants (eg, nitrous oxide), and synthesized compounds such as the "designer drugs," and marijuana.

Alcohol is by far the most commonly abused substance, particularly in older adult individuals with substance abuse. In the U.S., 13.8% of all adults have alcohol abuse or dependence at some point in their lives. The National Institute on Alcohol Abuse and Alcoholism has published a useful clinician's guide for helping patients who drink too much that can be accessed on the internet at: http://pubs.niaaa.nih.gov/publications/ practitioner/clinicians guide 2005/guide.pdf. Individuals who abuse alcohol may present with alcohol intoxication characterized by behavioral changes including expansive mood, social withdrawal, mood lability, irritability, and/or aggression. Physical/neurological symptoms such as diminished concentration, attention, and coordination may lead to falls and injury. Impulsivity and impairments in judgment and insight are associated with violence or accidents. Twenty-five percent of all suicides occur when individuals are intoxicated. Blood alcohol level closely approximates level of intoxication. In many communities, blood alcohol levels ≥80-100 mg/dL are considered unsafe and illegal for the operation of a motor vehicle. As alcohol is a short-acting sedative, in individuals with alcohol dependence, alcohol withdrawal begins 4 to 12 hours after the last drink. Clinical presentation includes tremor, tachycardia, hypertension, anxiety, and sweating. Symptoms continue over the next 1 to 2 days and may last up to 4 to 5 days. Some individuals may experience alcohol withdrawal seizures. Approximately 5% of individuals experience life-threatening withdrawal symptoms with delirium, termed delirium tremens or "DTs." Patients with chronic alcohol abuse may present with acute alcoholic encephalopathy (Wernicke's syndrome) or a persistent amnestic syndrome (Korsakoff's syndrome), which may be irreversible.

Stimulant drugs include cocaine and the synthesized amphetamine compounds. The two most commonly abused stimulants in the U.S. are cocaine and methamphetamine. Cocaine is an extremely addictive sub-

stance which is classified as a narcotic. Cocaine is used medically as a local anesthetic, particularly for ear, nose, and throat procedures. Although cocaine use appears to have generally decreased over the last decade in the United States, it remains an important public health hazard. A recent report from the Substance Abuse and Mental Health Services Administration notes that 500,000 individuals abuse cocaine weekly. Crack cocaine is an alkaloid or freebase cocaine, available in crystalline chunk form. This may be smoked to produce a rapid "high." The behavioral effects of cocaine are experienced almost immediately after drug administration (seconds to minutes) by intranasal, intravenous, or inhalation routes. Individuals become euphoric, talkative, and alert, possibly progressing to irritability, aggressiveness, agitation, and paranoia with frank psychotic symptoms. Physical symptoms of intoxication include hypertension, tachycardia, hyperthermia, and possibly cardiac arrhythmia, stroke, or seizures. As behavioral effects are generally short-lived, individuals using cocaine often repeatedly self-administer the drug. After cessation of cocaine use, individuals may experience a withdrawal syndrome of dysphoria, irritability, agitation, and severe drug craving.

Amphetamines and related compounds are synthesized sympathomimetic agents, used in medical settings to treat attention-deficit disorders, narcolepsy, and depression in some patients. The acute behavioral and physical effects resemble those described for cocaine, as does the withdrawal syndrome "crash." The smokable free-based form of methamphetamine ("ice" or "crystal meth") may last 10 times as long as effects of crack cocaine. As with cocaine withdrawal, individuals may be particularly prone to drug seeking, depression, and suicide. Use of methamphetamine has increased substantially in the United States, with highest geographic concentration of use in Hawaii, the West Coast, and the southern states. In 2004, 6.2% of high school seniors had reported life-time methamphetamine use. Methamphetamine use increases energy and alertness with a decrease in appetite. A "high" or "rush" is felt almost immediately, which can last for up to 12 hours. Side effects include seizures, hyperthermia, cardiac arrhythmia, abdominal distress, and shaking. Long-term use can be associated with feeling of skin crawling ("crank bugs"), anxiety, insomnia, and addiction.

Sedative/hypnotic drugs are agents that are central nervous system depressants. These include barbiturates, drugs such as chloral hydrate and meprobamate, and benzodiazepines. Drugs of this type are used to treat a variety of disorders in medical settings (see Clinical Issues in the Use of Anxiolytics and Sedative/Hypnotics) including anxiety, sleep distur-

bances, and agitation. In medical settings, the benzodiazepines have replaced other sedative/hypnotics due to their safety and effectiveness profile. Behavioral effects of sedative hypnotics include drowsiness, sleep, and decrease in agitation or anxiety. Physical symptoms include hypotension, impairments in coordination/balance, slurred speech, severe CNS depression, and respiratory depression. Individuals may become tolerant to the drug, requiring progressively larger doses for the same effect, and cross-tolerance to other CNS depressants, including alcohol, often develops. Heightened toxicity may occur when sedative/hypnotic drugs are used concurrently or with alcohol. Because of the wide use of sedative/hypnotic agents in medical settings, some patients may become tolerant to the effects of the drugs and self-initiate a pattern of increasing drug use/abuse. Patients who have developed dependence on sedative/hypnotics will experience a withdrawal reaction upon abrupt discontinuation of the drug. This is characterized by anxiety, restlessness, and gastrointestinal (GI) disturbance in the early phases (first day of symptoms), which may progress to hypotension, tachycardia, tremor, and agitation. Seizures and delirium may occur. Period of time from last drug dose until withdrawal symptom appearance varies depending on the active drug duration. This may be lengthy for long-acting drugs with active metabolites such as diazepam (up to 1 week) or brief (10-12 hours) with short-acting barbiturates.

Opioids refer to compounds derived from natural opium alkaloids (eg, opium and morphine), or synthesized compounds which have mechanisms of action similar to opium (eg, heroin, meperidine, and methadone). Heroin is not legally available in the United States; however, it is the most commonly abused opioid. Heroin is a dangerous drug, with 45% of all drug-related deaths in 1993 due to heroin. Synthetic opioids, called narcotics, have wide medical use in pain management of numerous disorders. Tolerance to opioid drugs develops quickly, and thus, abuse potential with this class of drugs is high. Acute behavioral effects include euphoria, sedation, and anorexia, while physical effects include constipation, pupillary constriction, emesis, and respiratory depression. Physical dependence often occurs within a week of receiving regular drug dosing. In addition to the risks associated with opioid intoxication and dependence, individuals that abuse intravenous opioid drugs, usually heroin, are at particular risk for transmission of human immunodeficiency virus (HIV) and hepatitis. These illnesses may be transmitted via shared needle use or sexual practices associated with a drug addiction lifestyle. Opioid overdosages are not uncommon due to the variable tolerance of individuals, difficulty in determining street drug purity, and the fact that

depression and suicide are often seen in opioid-abusing populations. Physical symptoms of overdosage are respiratory depression, hypothermia, pupillary constriction, and coma. Opioid withdrawal syndromes occur when a physically dependent individual abruptly ceases drug use. Symptoms include anxiety, diaphoresis, yawning, and rhinorrhea. Later, patients experience pupil dilation, tremor, muscle cramping, agitation, goose bumps, autonomic instability, and GI disturbance. Electrolyte imbalance may occur with GI disturbance and dehydration. Withdrawal symptoms may last 1 to 2 weeks depending on the drug of abuse.

Hallucinogens, also referred to as psychedelics or psychotomimetics, are agents that lead to hallucinations/illusions and enhanced awareness of consciousness. The group includes d-lysergic acid diethylamide (LSD), psilocybin, and mescaline. Hallucinogens may be natural or synthetic compounds that have no medical use in the United States. All have high abuse potential. Although hallucinogen use was more common in the 1960s, hallucinogen use in the U.S. population has been relatively stable over the last decade. Acute behavioral effects include hallucinations, paranoia, grandiosity, and perceptual changes such as depersonalization and slowing of time. Physical effects include tachycardia, hypertension, hyperpyrexia, and pupillary dilation. Most acute effects resolve over 8 to 12 hours; however, acute panic reactions during intoxication and flashbacks (spontaneous recurrences of drug-induced effects) may persist for months to years, while individuals with vulnerability to serious mental illness may exhibit persistent postintoxication psychosis. Tolerance develops quickly to behavioral effects of hallucinogens; however, there appears to be no physical dependence or withdrawal syndrome.

Inhalants are volatile gas compounds which produce CNS intoxication. Most commonly abused inhalants include glue and paint thinners (toluene), aerosols (nitrous oxide), and cleaning solutions (carbon tetrachloride). Inhalants are most commonly abused by the young, particularly teenage boys. Methods of administration include inhaling gases from a solvent soaked rag or breathing from a bag in which solvent has been placed. Aerosols may be directly inhaled. Acute behavioral effects occur within minutes and generally last up to 1 hour. These include euphoria, light-headedness, and disinhibition. Larger doses produce agitation, ataxia, and possibly arrhythmias and seizures. Headaches may occur several hours after use, as well as irritation of nasal mucosa and conjunctivitis. Tolerance develops quickly and withdrawal symptoms of tremulousness, tachycardia, agitation, and seizures have been reported when chronic users abruptly discontinue inhalant use. Chronic inhalant

abuse may be associated with neurological deficits such as encephalopathy, parkinsonism, or cerebellar ataxia.

Miscellaneous synthesized compounds include "designer drugs" such as 3,4-methylene-dioxy methamphetamine (MDMA or Ecstasy), 3,4-methylene-dioxy amphetamine (MDEA or Eve), and the veterinary tranquilizer phencyclidine (PCP or "Angel Dust").

The designer drugs are illegal compounds with no current medical use in the United States. Acute behavioral effects include euphoria and increased sociability. Physical effects may include cardiac arrhythmias and CNS neuronal damage. The designer drug l-methyl-4-proprionoxy-4-phenyl pyridine (MPPP) is associated with a parkinsonian syndrome in some users. Use of designer drugs has increased over the last decade or so as "club drugs," primarily used by adolescents/young adults.

PCP has been used on the streets since the 1960s. Currently, there is no human medical use for PCP in the United States. The drug is still abused with some degree of frequency in urban populations, but more often is taken as an adulterant in marijuana, heroin, or LSD. PCP is usually smoked with rapid onset of behavioral effects. These include agitation, psychosis, and violent behavior. Physical symptoms include nystagmus, drooling, tachycardia, muscle rigidity, and ataxia. Up to 66% of PCP-intoxicated individuals who present to emergency rooms are agitated and violent, often requiring seclusion, restraint, and pharmacologic management of severely disruptive behavior.

After tobacco, marijuana is the second most commonly smoked drug and the most commonly used illicit drug in the U.S. After a relative decline in the 1980s, marijuana use is now on a rise. Marijuana is usually smoked with little development of drug tolerance. The relative risk of marijuana use is approximately equal for men and women; thus, the historical assumption of male predominance does not apply to marijuana use. The active component is 9-tetrahydrocannibinol from the marijuana (Indian hemp) plant. Drug effects occur within 30 minutes, with behavioral symptoms of well-being and relaxation. Short-term memory and concentration may be impaired. Physical symptoms include increased heart rate, increased appetite, incoordination, and conjunctival redness. Occasionally, individuals may experience acute panic, confusion/disorientation, or "flashbacks" as may be seen with hallucinogens. Chronic heavy marijuana use has been associated with an amotivational syndrome characterized by decreased attention span, diminished ambition, distractibility, and impairments in social interactions.

Nicotine dependence and nicotine withdrawal are classified in DSM-IV as psychiatric disorders. Nicotine dependence/withdrawal can occur with

all forms of tobacco use including smoking of cigarettes, pipes, and cigars, as well as chewing tobacco and snuff. Smoking has been described as the most important preventable cause of disease, with 45% of smokers dying eventually of tobacco-induced disorders. Smoking is estimated to be responsible for 20% of all deaths in the U.S. and is associated with numerous medical illness, including lung, mouth, and other cancers, emphysema, cardiovascular disease, and peptic ulcer disease.[2] Smoking has also been associated with maternal/fetal complications. Most of the tobacco-induced disorders appear to be due to carcinogens and carbon monoxide in tobacco smoke, although nicotine itself may also cause health problems.

Most individuals who use tobacco in the U.S. are cigarette smokers. Mean age of smoking initiation is approximately 15 years.[3] Within a few years of daily smoking, most smokers develop dependence, with most smokers averaging about 20 cigarettes daily. Among older adult smokers, it is estimated that up to 87% are dependent on nicotine. When an individual who is dependent on nicotine stops or reduces nicotine intake, they typically experience withdrawal symptoms within 24 hours. Symptoms may include depressed mood, insomnia, irritability, anxiety, restlessness, diminished concentration, and lowered heart rate. Appetite may be increased, with weight gain (usually 2-3 kg) often occurring during the first few months after smoking cessation. Individuals who use/abuse alcohol and those with mood disorders or attention-deficit disorders are more likely to be smokers. Smoking may also affect blood levels of psychiatric medications, for example, smoking decreases haloperidol and clozapine levels by 30%. In the United States smoking has been increasingly banned in public buildings. It has been reported that cigarette smoking is the leading cause of preventable death in the U.S., causing over 430,000 premature deaths.

General Treatment Recommendations

Individuals with substance abuse are often both physically and psychologically impaired. Management and treatment of substance abuse can be divided in the main areas of:

- treatment of acute intoxication/overdose
- treatment of withdrawal
- general treatments for psychological addiction/rehabilitation

Additionally, individuals who abuse substances frequently have comorbid psychiatric disorders which affect final outcome. Proper diagnosis and

treatment of comorbid psychiatric disorders improve outcome in nearly all cases.

Significant progress has been made in the development of pharmaco-therapies for substance use disorders. Effective medications are available for tobacco, alcohol, and opioid use disorders.

Psychosocial treatments include inpatient care (now increasingly rare in today's managed care settings), outpatient therapies which may be in individual or group settings, and self-help residential treatment programs (therapeutic communities).

Numerous studies have demonstrated that psychotherapy added to pharmacologic management promotes abstinence better than pharmaco-logic management alone.

Alcohol

Intoxication/Overdose

Alcohol intoxication may be severe with extreme usage, potentially leading to respiratory depression, coma, and death. These individuals require close monitoring in an intensive care setting. An idiosyncratic reaction of severe behavioral symptoms occurring after relatively low level alcohol ingestion has been reported. Symptomatic support with environmental protection, and possibly the addition of low-dose antipsy-chotic medication, may be beneficial in these individuals (eg, haloperidol 1-2 mg orally or IM).

Withdrawal

Symptoms can begin within 6 to 48 hours postcessation and persist up to 5 days. About 5% of these patients will develop full-blown delirium tremens. The mortality rate for delirium tremens is 1 to 5%.[4] Benzodi-azepines are the most effective treatment for alcohol withdrawal. For tremor and mild agitation, an oral benzodiazepine such as lorazepam 1-2 mg every 4 to 6 hours is generally effective. Individuals with more severe agitation or hallucinations may require IM or IV medication. Chlordiaz-epoxide (25-100 mg orally) can be administered as an alternative to lorazepam. Phenobarbital (5 mg/kg IV or 15 mg of phenobarbital for each 30 mL "1 ounce" of 80-100 proof) may be used for resistant cases. Phenytoin is not useful in treating ethanol withdrawal seizures. Trazodone (50-150 mg orally at night) can be used as a sleep aid. Individuals with delirium tremens (or DTs) should be in closely observed medical settings (hospitalized) and must receive maintenance benzodiazepine treatment until behavior and autonomic symptoms (tachycardia, hypertension)

stabilize. Dosage should then be titrated as clinically indicated. In very resistant cases, a propofol infusion (40 mg IV followed by an infusion of 50 mcg/kg/min) can be considered with ventilatory support.[5] Sodium pentobarbital (with appropriate airway management) is also a reasonable alternative. The initial dose is 3-5 mg/kg IV, followed by a 100 mg/h infusion for sedation. Most cases of DTs may be avoided if treated with oral or IM benzodiazepines when the patient is in the early alcohol withdrawal phase. Vital signs should be closely monitored as an index of severity of withdrawal. Intravenous fluid hydration with D_5 0.9% NS at 300-1000 mL/h should be instituted if significant dehydration is present.[6] A supportive, nonthreatening, and therapeutic environment is helpful as patients with alcohol withdrawal are often frightened and severely anxious. Treatment with benzodiazepines may be decreased in both dosage and frequency over the next several days as withdrawal symptoms resolve.

Acute alcoholic encephalopathy (Wernicke's syndrome) should be managed with thiamine 50 mg/day IM or 100 mg/day orally for 1-2 weeks. Serum glucose, phosphate, and magnesium should be monitored. The chronic amnestic syndrome associated with long-term alcohol abuse (Korsakoff's syndrome) may improve with thiamine 100 mg/day continued for 6 to 12 months, although most patients have limited cognitive recovery. Antipsychotics are generally best avoided in alcohol withdrawal as they may lower seizure threshold. However, in cases of failure of benzodiazepines to control paranoid behavioral symptoms or hallucinations, judicious use of antipsychotic medication may be helpful.

General Treatment

Most clinicians agree that complete abstinence from alcohol is the cornerstone of successful alcohol abuse treatment; however, in some patients reduction in drinking may be a short-term goal that is more readily achievable. Psychotherapy that focuses on drinking behavior and alternative behaviors is generally the most effective intervention. This includes individual, group, marital, and family therapies. Self-help groups such as Alcoholics Anonymous (AA) may be extremely helpful.

Specific biologic interventions that may be adjunctive in promoting alcohol abstinence are disulfiram, naltrexone, acamprosate, and some psychotropic drugs. Disulfiram competitively inhibits the enzyme aldehyde dehydrogenase, so that subsequent alcohol ingestion leads to serum acetaldehyde accumulation and resultant symptoms of flushing, feeling overheated, nausea, and general malaise. Dizziness, palpitations, and hypotension may occur. Symptoms generally persist for 30 to 60 minutes

and may be useful in motivated, healthy patients in assisting with abstinence. Disulfiram must be taken daily, generally in the morning, and is usually prescribed at a dosage of 125-250 mg/day. Although some individuals benefit from the addition of disulfiram to an alcohol treatment regimen, its use must be weighed against the medical risks (severe hypotension, hypocalcemia, respiratory depression) if the individual continues to drink while on disulfiram. Disulfiram should *never* be given to an individual without their knowledge.

Naltrexone, a narcotic antagonist, may also be a useful adjunct as part of an alcohol treatment regimen. Naltrexone at doses of 50 mg/day may reduce drinking in recovering alcoholics. Adverse effects may include hypertension, GI disturbance, and sedation. Rarely, liver functioning may become impaired, and hepatic screening and monitoring should be done concurrently. A long-acting once-monthly formulation of naltrexone may boost adherence with treatment.

In 2004, the FDA approved acamprosate for treating alcohol-dependent individuals seeking to continue to remain alcohol free after they have stopped drinking. Acamprosate may reduce alcohol craving and the amount that alcoholics drink when they do drink. The most common adverse effects are diarrhea, nausea, vomiting, and abdominal pain.

Additional psychotropic medications that have been reported to be useful in alcohol treatment include antidepressants such as the serotonin reuptake inhibitors fluoxetine and citalopram and the 5-HT$_3$ antagonist ondansetron. Additionally, treatment of existing comorbid psychiatric disorders such as major depression, bipolar disorder, or post-traumatic stress disorder (PTSD) will usually substantially improve outcome.

Baclofen

Intoxication

Baclofen is a gamma aminobutyric acid (GABA) type B receptor agonist. Intoxication (due to oral ingestion over 5 mg/kg) is characterized by marked central nervous system depression, hypotonia, seizures, and tachycardia. Flumazenil can be useful in treating coma due to oral overdoses, while physotigmine has been utilized to alleviate drowsiness due to intrathecal baclofen toxicity. It should be noted that baclofen has been used to treat alcohol withdrawal.[7,8]

Withdrawal

Baclofen withdrawal syndrome usually occurs within 12 to 72 hours following dose cessation. The syndrome is similar to the sedative-

hypnotic withdrawal syndrome with agitation, delusions, spasticity, rhabdomyolysis, paranoia, psychosis, pruritus, hallucinations, hypertonia, fever, and seizures. Benzodiazepines (diazepam 5-10 mg orally every 6-12 hours) are the mainstay of baclofen withdrawal therapy. For acute intrathecal baclofen withdrawal, baclofen (10-20 mg orally every 6 hours) and cyproheptadine (4-8 mg orally every 6-8 hours) can also be utilized with the latter agent particularly effective in treating pruritus.[9] Reinstatement of baclofen will usually result in symptom resolution within 48 hours. Dantrolene (10 mg/kg) has been used to treat baclofen withdrawal induced hyperthermia.

Caffeine

Intoxication

Caffeine is a methylxanthine that produces hyperadrenergic signs in overdoses (hypertension, tachycardia, seizures, hyperthermia, hypokalemia, and tremors). Treatment is focused on seizure control with benzodiazepines or Phenobarbital. (Phenytoin should be avoided.) Multiple doses of activated charcoal can aid in enhancing elimination of caffeine as can charcoal hemoperfusion.

Withdrawal

Physical dependency to caffeine does exist with withdrawal symptoms usually occurring within 12 to 24 hours following cessation and peaks at 20 to 51 hours and may last for 1 week. A daily dose over 235 mg (about 2.5 cups of coffee/day) can increase the risk for likelihood of withdrawal. While lethargy and weakness may occur, facial flushing and severe headaches predominate this syndrome and may last as long as 9 days. Other symptoms include yawning, rhinorrea, and irritability.[10] Symptoms correlate with the amount ingested prior to cessation. Treatment focuses on a gradual reduction of caffeine intake over several days. Caffeine tablets may be useful in headache treatment.

Cocaine

Intoxication/Overdose

The symptoms of cocaine intoxication are similar to alcohol. In cases of high-dose use or when intravenous route has been used, symptoms may be severe, including extreme anxiety, paranoia, and hallucinations. Severe hypertension, hyperthermia, and arrhythmias may occur. Management of autonomic hyperarousal may benefit from benzodiazepines. Phentolamine may be beneficial in hypertensive crisis. Other supportive measures

include close monitoring of vital signs, maintenance of fluid status, and ambient cooling for hyperthermia.

Withdrawal

Cocaine withdrawal is characterized by the three following phases: (1) an initial "cocaine crash" phase (fatigue, insomnia, depression) lasting for 1 to 2 days; (2) withdrawal phase (dysphoria, anxiety), followed by (3) an extinction phase. An intense craving for cocaine can occur at any time. Cocaine withdrawal symptoms generally are managed supportively with no specific identified pharmacologic treatments. Intense cocaine cravings may lead individuals to self-medicate with cocaine or other illicit substances.

General Treatment

As with alcohol and other drugs of abuse, abstinence from cocaine is essential in maintaining successful treatment. There are an estimated 1.7 million cocaine users in the U.S. While there are currently no FDA-approved pharmacotherapies for cocaine dependence, promising research findings have been reported for disulfiram, tiagabine, and other novel treatments. Psychotherapy has been proven to be helpful, while some pharmacotherapies (desipramine, amantadine) have suggested efficacy in some individuals with reduced cocaine craving, dysphoria, and drug use. Comorbid psychiatric illness should be treated as needed to optimize outcome.

Opioids

Intoxication/Overdose

Most individuals with self-induced opioid intoxication (as with other types of illicit substance intoxication) do not present for treatment unless distressing physical or behavioral symptoms occur. Overdosage situations, however, are relatively common among chronic opioid drug abusers. Anoxia, coma, and death may occur unless intervention treatment is initiated. Initial measures include airway protection, vital sign monitoring, and administration of naloxone, an opiate antagonist. Naloxone may be given at an adult dose of 0.4-2 mg IV and should reverse overdose symptoms within 2 minutes. Dosage may be repeated twice more at 5-minute intervals, if necessary. Alternatively, nalmefene at doses of 0.5 to 1 mg in up to 10 boluses can reverse opioid toxicity rapidly. Treating clinicians should also be alert to the possibility of concomitant substance overdose (eg, barbiturates) or medical conditions that may

contribute to respiratory depression (eg, traumatic head injury). Patients with good response to naloxone may require repeated dosing over the next several hours as duration of action of naloxone generally does not exceed 4 hours. Care should be taken when using naloxone to guard against precipitating a withdrawal reaction in opioid-dependent patients.

Withdrawal

Withdrawal symptoms occur within 6 to 12 hours after ingestion of last drug dose in opioid-dependent persons. Treatment of opioid dependence involves management of primarily acute physical symptoms in the acute phase. For acute phase withdrawal (detoxification), the synthetic opioid methadone has been used successfully by many clinicians who treat substance abuse disorders. In patients who begin to exhibit signs and symptoms of opioid withdrawal (hypertension, tachycardia, sweating, lacrimation, rhinorrhea), methadone 1 mg orally is given as needed over the next 24 hours for a maximum of 10-40 mg over the first day of detoxification treatment. Once maintenance dosage requirements are determined (total methadone dose required to contain symptoms over the first 24 hours of detoxification), this dose can be given for an additional 2 days; then, a slow daily taper initiated until the individual is to be maintained off opioid drugs. Other minor tranquilizers such as chlordiazepoxide (25-50 mg orally twice daily) or clorazepate (3.75-7.5 mg orally twice daily) can be used to treat opiate withdrawal during the first 72 hours. Ultra-rapid opioid detoxification has been used since the 1980s with varying success.[11] Using principles of general anesthesia in combination with an opiate antagonist, followed by naltrexone maintenance therapy, 1-month abstinence rates vary from 53 to 93%.

Some clinicians use the nonopioid antihypertensive clonidine to treat symptoms of acute opioid withdrawal. Clonidine may be used alone or concurrently with methadone. For acute detoxification, clonidine 0.4-2 mg/day may be used. Due to its antihypertensive properties, pulse and blood pressure must be closely monitored. Some patients experience excessive sedation with clonidine, which may be moderated by dosage adjustments. Gastrointestinal cramps can be treated with dicyclomine (20 mg orally every 4-6 hours as needed), while nausea can be safely treated with prochlorperazine (10 mg orally or IM every 6 hours as needed). Loose stools may respond to loperamide (2 mg orally as needed, to a maximum daily dose of 6 mg). Trazodone (50-150 mg orally at night) can be given as a sleep aid.

An alternative compound, buprenorphine, a partial opioid antagonist, may be useful in acute detoxification situations. Like methadone, dosage

should be customized to the individual and tapered and eventually discontinued as tolerated.

General Treatment

Treatment of chronic opioid dependence involves both treatment of physical withdrawal symptoms, plus psychological dependence on the drug. Commonly utilized pharmacotherapies include the opioid agonists methadone and buprenorphine. Psychosocial and psychotherapeutic treatments are essential in promoting the lifestyle changes needed to prevent relapse. Until recently, opioid maintenance treatment could only be provided by licensed opioid treatment programs. Recent changes in legislation introduced office-based opioid maintenance treatment programs with buprenorphine. These changes are anticipated to increase treatment access. It is estimated that there are about 900,000 chronic illicit opiate users in the U.S. and only about 20% of these users are enrolled in treatment programs.

Methadone maintenance has proven efficacy in some groups of opioid abusers. As with acute phase treatment, chronic methadone treatment dosage/format must be tailored to the individual. Usual daily oral dosage ranges from 30 to 100 mg/day. Generally, patients must come to the clinic daily (usually morning) to receive methadone. Other interventions involved in clinic treatment may include counseling, urine drug testing, vocational rehabilitation, etc. When used successfully, methadone maintenance reduces illegal drug use and reduces the medical, legal, and societal ramifications associated with the illicit drug culture.

Buprenorphine is a partial μ-opioid agonist and weak K-opioid antagonist. In typical doses used in clinical settings buprenorphine acts similar to methadone. At higher doses, buprenorphine effects plateau, acting as an opioid antagonist. This ceiling effect decreases overdose risk. Buprenorphine is FDA approved for treating opioid dependence. Buprenorphine is available as a sublingual tablet either alone or as a combination tablet containing buprenorphine and naloxone in a ratio of 4:1. Because of its partial agonist action, buprenorphine may precipitate withdrawal in opioid-dependent persons. Common daily dose ranges from 4 to 24 mg/day. Potential adverse effects include abdominal pain, constipation, nausea, vomiting, headache, and sweating.

An alternative strategy in managing long-term opioid abuse treatment is the use of opioid antagonists. Naltrexone, a long-acting (72 hours) antagonist, blocks the euphoric effects of opioids and may be taken three times/week at dosages of 100-150 mg. Theoretically, the use of naltrexone discourages persons from opioid use as it eliminates the subsequent

CNS effects. In clinical practice, poor adherence and high dropout rates limit the usefulness of naltrexone for maintenance treatment of opioid dependence. Naltrexone works best with highly motivated individuals with good psychosocial support as there are no physical incentives (withdrawal symptoms) to continue taking opioid antagonist on a long-term basis.

Sedative/Hypnotic

Intoxication/Overdose

Severity of symptoms of sedative-hypnotic intoxication depends on drugs used, route administered, and tolerance of the individual to the drug. Sequelae of overdose are greatly worsened when alcohol or multiple sedative/hypnotics are combined. Respiratory depression is the major danger and successful management includes respiratory and cardiac support. Margin of safety in benzodiazepine overdose is much greater compared to barbiturate overdose where unintentional lethal dosing is not uncommon. In addition to standard supportive measures (vital sign monitoring, gastric lavage, hospitalization, etc), patients with overdose should be closely assessed for suicide risk and intent.

Withdrawal

As with toxicity, severity of withdrawal symptoms is dependent on a variety of clinical factors including duration of drug use (usually maintenance of 1 month or longer for dependence to develop) and tolerance of the individual. Withdrawal of sedative-hypnotic is generally managed by either (1) gradual reduction of sedative substance, or (2) substitution with a long-acting benzodiazepine or phenobarbital with subsequent taper and eventual discontinuation.

Gradual discontinuation from sedative-hypnotic is best accomplished with motivated patients in settings with good psychosocial supports. The rate of drug taper should be tailored to the individual, with slower titrations generally being most successful.

For benzodiazepine-dependent patients, substitution of an equivalent dose of long-acting benzodiazepine (eg, clonazepam) with gradual downward titration will promote reduction of withdrawal effects over time. As with other addiction treatments, concurrent psychosocial treatments will optimize clinical outcome.

For barbiturate-dependent individuals, the clinician should attempt to determine the patient's daily dose of barbiturates and stabilize withdrawal symptoms with the barbiturate. As many individuals who abuse sedative-

hypnotics may be unreliable in providing accurate daily use information, the clinician may elect to assess barbiturate tolerance with a challenge dose of the short-acting barbiturate pentobarbital. This should be done in hospital settings. The patient undergoing sedative withdrawal is given 200 mg pentobarbital and observed for resolution of withdrawal symptoms and mild intoxication. Patients in whom this occurs may then be maintained on pentobarbital 100-200 mg every 6 hours. Patients who are not intoxicated on the initial challenge dose of 200 mg are given an additional 100 mg pentobarbital every 2 hours (for a maximum of 500 mg) until mild toxicity develops. Maintenance pentobarbital dose is then determined based on total amount of barbiturate needed to cause mild intoxication. Once stabilization is achieved, the clinician can then taper the dose by 10% daily. Alternatively, phenobarbital, a long-acting barbiturate, may be substituted for pentobarbital. Phenobarbital has the advantages of less frequent dosing, fewer fluctuations in blood level, and anticonvulsant activity. The equivalent dosing of 30 mg phenobarbital as a barbiturate is 100 mg pentobarbital, 100 mg secobarbital, 100 mg amobarbital, or 60 mg butabarbital. Other sedative-hypnotic agents equivalent to 30 mg phenobarbital in the withdrawal state include chloral hydrate 500 mg; ethchlorvynol 350 mg; glutethimide 250 mg; mepro-bamate 400 mg; methaqualone 300 mg; methyprylon 100 mg.

General Treatment

Psychotherapeutic interventions appear to be the most effective long-term treatments in sedation/hypnotic abuse.

Benzodiazepine

Intoxication

Central nervous system depression with hypotension due to vasodilation and concomitant respiratory depression are the predominant sequelae. The mainstay of therapy is supportive with particular attention to ventilatory and circulatory support. Flumazenil (children 0..01 mg/kg; maximum dose of 0.05 mg/kg or 1 mg, whichever is lower; adults: up to 5 mg) is effective in reversing the sedative effects of benzodiazepines.

Withdrawal

Tolerance can develop rapidly in benzodiazepine therapy and from 15 to 44% of chronic users experience withdrawal symptoms when their benzodiazepine dose is decreased. Patients who take benzodiazepines for greater than 3 months are at risk for withdrawal. The onset of symptoms

may be as short as 1 day for the longer acting benzodiazepines (ie, diazepam). Symptoms may last for 6 weeks. Symptoms are due to neuronal excitation and may include anxiety, insomnia, fever, tremor, nausea, tinnitus, myalgias, seizures, vomiting, and diaphoresis. Treatment consists of reinstitution of a long-acting benzodiazepine with a gradual taper (over a period of 6-8 weeks). In cases of severe symptomatology, an intravenous infusion of diazepam (at 20 mg/h or more) in a monitored setting may be initially required. Phenobarbital 30 mg equivalency for benzodiazepines includes alprazolam 0.5 mg; clorazepate 7.5 mg; chlordiazepoxide 25 mg; diazepam 5 mg; flurazepam 30 mg; lorazepam 1 mg; oxazepam 15 mg; temazepam 60 mg; triazolam 0.5 mg; clonazepam 0.25 mg. One-fourth of this calculated dose is administered and the dose is increased as necessary. The phenobarbital dose can be tapered after the patient is stabilized for 48 hours at a rate of 10% of the dose daily. Propranolol (20 mg 3-4 times/day) can be instituted on day 5 and continued for 2 weeks as an adjunctive agent.

Gamma Hydroxybutyrate (GHB)/Gamma Butyrolactone (GBL)

Intoxication

CNS predominates and the mainstay of management is respiratory support. Hypothermia, hypotension, and seizures may also occur. Atropine can be used to treat bradycardia. Sudden arousal is usually noted 5 to 8 hours postingestion.

Withdrawal

Withdrawal symptoms may occur with constant use for a period of over 2 months, especially if there is a recent dose escalation.[12,13] CNS hyperactivity such as insomnia, tremor, delirium, psychosis, and auditory/visual hallucinations occurs within 12 hours of cessation of doses. Duration of symptoms ranges from 5 to 15 days. Treatment is supportive with lorazepam and/or haloperidol (5 mg) effective for treatment of delirium or psychosis. Often large doses of benzodiazepines are required.[14] Pentobarbital (initial dose 2.5-5 mg/kg IV) can also be given to treat resistant symptoms.[15]

Selective Serotonin Reuptake Inhibitors (SSRIs)

Intoxication/Overdose

Acute signs and symptoms of overdose include nausea/vomiting, sinus tachycardia, tremors, and lethargy. Seizures may occur in Citalopram,

Escitalopram, Venlafaxine and bupropion overdoses.[16] Characteristic of these ingestions is QTc prolongation on electrocardiogram. Treatment is supportive.

Withdrawal

Withdrawal occurs most frequently upon abrupt cessation with paroxetine, sertraline, fluoxetine, and venlafaxine.[17,18] Paroxetine appears to be the SSRI with the highest incidence of withdrawal reactions at a rate of 300 cases per million prescriptions. Citalopram appears to exhibit the lowest incidence of withdrawal. Symptoms usually begin within 1 to 2 days and involve dizziness, ataxia, anorexia, diarrhea, flu-like symptoms, anxiety, diaphoresis, parethesias, tremor, and sleep disturbances. Symptoms may last as long as 2 to 3 weeks. Temporary reinstitution of an SSRI with gradual tapering over several weeks is suggested.[19] Ginger root, 1100 mg 3 times/day for 1 to 2 weeks has been noted to be efficacious for sertraline withdrawal.

Stimulants

Intoxication/Overdose

Intoxication/overdose management involves reducing autonomic hyperactivity (tachycardia, hypertension) and managing CNS symptoms (agitation, psychosis/delirium, or seizures).[20] Supportive measures such as appropriate hydration, vital sign monitoring, and cooling for hyperthermia are indicated. Anxiolytics or antipsychotics may be useful on a short-term basis, and a supportive, low-stimulation environment will reduce CNS irritability.

Withdrawal

Amphetamine withdrawal is generally treated supportively. The judicious use of antipsychotic medication may be of benefit to patients with post-amphetamine psychosis. Antidepressant medications may help the depressive symptoms of withdrawal.

General Treatment

Psychotherapeutic interventions appear to be the most effective long-term treatment. The current literature suggests that cognitive behavioral therapy may help with methamphetamine addiction.

Hallucinogens

Intoxication

Individuals who experience toxic delirium, panic reactions, or psychosis associated with hallucinogens require a supportive environment (low stimulation with supervision) and may benefit from judicious dosing of anxiolytics (eg, diazepam 5-10 mg orally).[21]

Withdrawal

Physical dependence and withdrawal symptoms have not been reported.

General Treatment

Psychotherapeutic interventions appear to be the most effective in long-term treatment.

Inhalants

Intoxication

CNS effects of intoxication usually resolve within minutes to hours of inhalant use. Toxic effects depend on the solvent used and may require emergency treatment for arrhythmias or CNS hyperactivity (seizures). Some agents (such as toluene) produce renal damage and renal functioning should be monitored. Intoxication treatment is generally supportive.

Withdrawal

Withdrawal reactions occur rarely as most inhalant use is relatively short-lived. Symptoms that may occur are generally treated supportively with concurrent psychosocial interventions.

General Treatment

Psychotherapeutic interventions are generally most effective. Due to the young age of most patients, family therapy is often also indicated.

Synthesized Compounds

Intoxication/Overdose

PCP toxicity is best managed in a low-stimulation, secure environment. Benzodiazepines and careful use of antipsychotic medication may be helpful for the severe agitation/aggression sometimes seen in PCP intoxication. Some clinicians advocate promoting rapid drug excretion with ammonium chloride or ascorbic acid. However, urine acidification is controversial as it may cause more problems in patients with liver or renal

disease. Most PCP toxic reactions resolve within 1 to 3 days, but behavioral symptoms may persist for 2 weeks or more.

In acute intoxication situations, MDMA has been associated with cardiac arrhythmias, suggesting a need for close intensive medical monitoring. Additionally, some designer drugs may contain contaminants which have been associated with permanent neurologic damage.

Withdrawal

Physical dependence on PCP generally does not occur, although psychological dependence may be associated with drug craving and relapse.

General Treatment

Psychotherapeutic interventions are generally most effective in the long term. Little is known about long-term treatment of designer drug abuse.

Marijuana

Intoxication

The incidence of acute adverse reactions to marijuana is quite low. In rare cases, individuals may experience acute panic, toxic delirium, or flashbacks. These generally remit spontaneously within 12 to 48 hours. Management may include anxiolytics of antipsychotics if behavioral symptoms are severe.

Withdrawal

Tolerance generally does not develop to marijuana, although heavy daily users may experience withdrawal symptoms of insomnia, diaphoresis, dysphoria, irritability, tremor, and nausea. Symptoms peak at 48 hours of abstinence and persist for 96 hours. There is no recognized withdrawal regimen.

General Treatment

As with other substance abuse disorders, individuals should receive psychosocial rehabilitation and there should be assessment and treatment of any coexisting psychiatric disorders.

Nicotine

Intoxication/Overdose

Nicotine intoxication from tobacco use is rare. Excess nicotine from nicotine replacement therapies used in smoking cessation (ie, nicotine

gum) may occasionally cause adverse effects such as nausea, headaches, or cardiac abnormalities.

Withdrawal

Withdrawal symptoms begin within 6 to 12 hours and generally peak 24 to 72 hours after smoking cessation. Most symptoms last for approximately 1 month, although craving can persist for 6 weeks or longer. Smoking cessation is associated with slowing on electroencephalogram, and decline in metabolic rate, including mean heart rate decline of 8 beats/minute. Blood levels of some antidepressants (eg, clomipramine, desipramine, doxepin, imipramine, and nortriptyline) may increase as may some antipsychotic medications (eg, clozapine, fluphenazine, haloperidol, olanzapine) and some anxiolytics (eg, oxazepam, diazepam).

The most successful treatment of nicotine withdrawal frequently includes both psychosocial and pharmacological interventions. Patients must generally be committed to quitting, and most clinicians advocate abrupt cessation of tobacco rather than gradual reduction. Approximately 33% of adults who smoke make an attempt to stop smoking each year. Relapse is common, particularly among those who attempt to quit smoking on their own without formal treatment. Approximately 50% of smokers eventually quit, although individuals with histories of anxiety or mood disorders or of schizophrenia are less likely to stop smoking. Most smokers require five to seven attempts at smoking cessation before they eventually quit for good. Psychosocial treatments include behavior therapies (relapse prevention, relaxation, stimulus control among other techniques), education (group or individual), and hypnosis. Pharmacotherapies include nicotine replacement therapy, nicotine antagonists, agents that mimic nicotine effects, aversive therapies, and symptomatic management. Nicotine replacement therapy and antidepressants for symptomatic management are among the most commonly utilized pharmacologic measures.

Nicotine replacement provides the nicotine-dependent patient with nicotine in a form that is not associated with the carcinogenic elements in tobacco. Nicotine gum, a nicotine lozenge, transdermal nicotine patches, nicotine nasal spray, and nicotine inhalers are available for smoking cessation. Nicotine gum, now available over the counter, consists of 2-4 mg of nicotine in a polacrilex resin designed to be slowly chewed for 20 to 30 minutes. Nicotine absorption peaks 30 minutes after initiation of gum use. Most common adverse effects are GI complaints (nausea, anorexia) and headache. Although nicotine replacement has been used for relief of withdrawal symptoms, some patients utilize these therapies long-term.

Nicotine patches consist of nicotine impregnated into an adhesive patch for

transdermal application. Patches are applied daily each morning upon quitting smoking with starting dosages of 21-22 mg/24-hour patch and 15 mg/16-hour patch. Patients should not smoke cigarettes while on patches as nicotine toxicity may occur. Typical treatment duration is 6 to 8 weeks. The nicotine inhaler contains a replaceable component that delivers nicotine in inhaled air. Unlike cigarettes, which deliver nicotine directly into the arterial blood in the lungs, the inhaler delivers nicotine into the buccal mucosa. Some clinicians advocate the use of combination therapy in the treatment of nicotine dependence. One general approach is to combine a long-acting treatment such as bupropion with a shorter acting treatment such as nicotine gum.

In addition to nicotine replacement, some antidepressants (bupropion, nortriptyline, doxepin, and desipramine) have been shown to improve the chances of nicotine abstinence. Sustained-release bupropion hydrochloride has been approved by the FDA for smoking cessation. In addition to reducing nicotine withdrawal symptoms, bupropion S-R may diminish weight gain. Some clinicians utilize both bupropion and nicotine replacement concurrently.

Some clinicians utilize clonidine at dosages of 0.1-0.4 mg/day for nicotine withdrawal in individuals who fail or are unable to tolerate other symptomatic treatment or nicotine replacement. However, use of clonidine for smoking cessation is often limited by adverse effects including sedation, dizziness, and dry mouth.

General Treatment

The Department of Health and Human Services has devised a systemic approach based on the "5 A's." This consists of the following:

1. **Ask** and record smoking status. In several surveys, only about 50% of physicians asked patients about their tobacco use.
2. **Advise** to stop. Direct recommendation from a physician produces quit rates of 7% to 10%.
3. **Assess,** evaluate whether the patient is willing to quit smoking at this time. The goal is to provide motivation without "nagging."
4. **Assist** the patient in addressing cessation. Identifying a quit date may assist in obtaining commitment to quit. Patients who are unable or unwilling to commit to quitting may benefit from educational materials at this time.
5. **Arrange** follow-up. This should occur within 3 days as the first several days after quitting are a critical period in relapse risk.

Most pharmacotherapies are primarily utilized during the initial period of quitting tobacco use. Psychological treatments/lifestyle changes while also utilized during nicotine withdrawal must also become long-term interven-

tions. Although biologic treatments do not require concurrent psychological therapies, the best outcome is usually associated with combined treatment.

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