5 Drug Intoxication in the Emergency Department

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Introduction

Substance use is highly prevalent among patients presenting to emergency departments (EDs). According to the Substance Abuse and Mental Health Services Administration (SAMHSA) Drug Abuse Warning Network report, in 2011, there were approximately 2.5 million drug-abuse-related ED visits nationwide [1]. Twenty-five percent of the total drug-related ED visits involved illicit drugs, and 28% involved pharmaceuticals. The most common illegal drugs of abuse were cocaine, marijuana, and heroin. Between 2004 and 2011, the most massive pharmaceutical increase was recorded for oxycodone (220%) [1] (Fig. 5.1).

Approximately one in eight visits to EDs in the United States involves mental and substance-use disorders [2]. Between 2007 and 2011, the rate of ED visits related to mental and substance-use disorders increased by over 15% [3]. The majority of drug-related ED visits were made by patients 21 years and older (81%). The rates for cocaine use are the highest among individuals aged 45–54 and for heroin in the age group 35–44. Race/ethnic differences in substance use are described best as in the DAWN 2011 report: White individuals preferentially used heroin and methamphetamine, compared with Black individuals (4.6 times and 8.5 times, respectively), while Black individuals preferentially used cocaine, compared with White individuals (1.2 times) [4].

Existing studies typically address substance use in global terms and rarely elaborate on whether a patient presented to an ED in a state of intoxication or withdrawal. According to one study, 32% of patients came into the psychiatric emergency service (PES) in a state of acute alcohol or drug intoxication, and 17% had a primary diagnosis of substance abuse or dependence [5]. This study also reported that these patients consumed considerable time and resources, as 64% of the patients were suicidal and 26% were hospitalized.

Psychiatric Comorbidity

Substance use complicates the differential diagnosis of the ED patient, as the effects of drugs can mimic a variety of psychiatric syndromes. For example, in a patient who presents with psychotic

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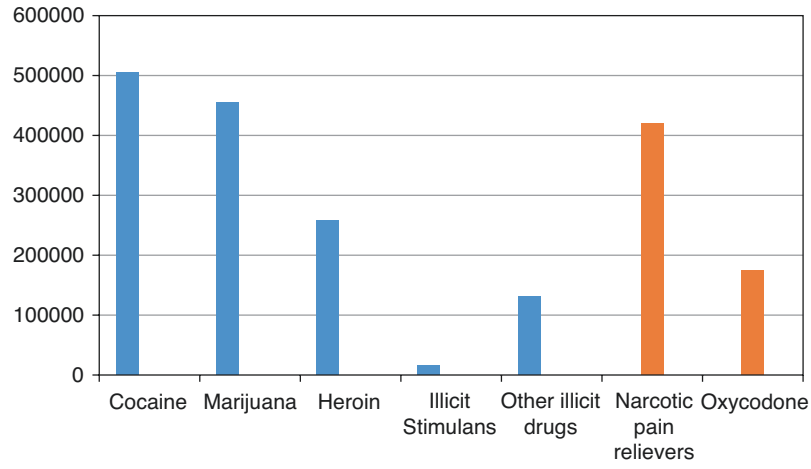

Fig. 5.1 Drug-related emergency department visits: 2011. (Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN) [1] (*2011 was the last year that the DAWN report was generated))

symptoms and who recently has used an illicit drug, often it is unclear whether the psychosis is a direct consequence of a substance or whether the patient has a primary psychotic disorder that coincides with drug use. One study that addressed this issue reported that in as many as 25% of patients who presented with psychotic symptoms, the PES clinicians attributed psychotic symptoms to a primary psychotic disorder that later was determined to be a substance-induced psychosis. The potential consequences of misdiagnosing psychosis in ED or PES are severalfold: unnecessary hospitalization, inappropriate use of antipsychotics, lack of appropriate follow-up, and inattention to substance-use treatment [6]. The literature on first-episode psychosis indicates a high association with substance-use disorders (SUDs). Approximately one-half of first-episode patients have a history of cannabis abuse or dependence, and one-third have a current cannabis-use disorder [7].

Substance use is highly prevalent among patients with psychiatric disorders, and drug or alcohol use often contributes to frequent ED visits. Patients with comorbid psychiatric and SUD have up to 5.6 times greater use of ED services [8].

Alcohol and substance-use disorders are associated with suicide risk [9]. Individuals with a SUD are about six times more likely to report a lifetime suicide attempt than those without a substance-use disorder. One study found particularly high suicidality among cocaine users who presented to an urban PES [10]. Another study evaluated the relationship of alcohol and drug use and severity of suicidality in patients who were admitted through an urban PES to an acute psychiatric inpatient unit. In the most severely suicidal group, 56% had substance use or dependence [11]. Particularly vulnerable groups for the effects of alcohol and substances include youth (ages 12–17), and veterans. A recent study showed that veterans with a substance-use disorder are approximately 2.3 times more likely to die by suicide than those who are not substance users. Concerning specific SUDs, the suicide rate associated with sedative use was the highest (4.7 times greater), followed by amphetamine (2.6×) and opioid (2.4×) use [12]. The astounding finding in this study is that women had 11 times higher likelihood of dying from suicide associated with sedative-hypnotics than men (hazard ratio 11.4 vs. 4.7).

There is an active link between depression and suicidality in individuals with comorbid mood and substance-use disorders [13]. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), an extensive national study conducted among adults in the US, found that among individuals with an anxiety disorder, almost 15% had SUD. Similarly, among individuals with an SUD, nearly 18% had alcohol use disorder [14]. The effects of comorbid alcohol and SUD on premature death were found to be the highest among individuals with bipolar disorder [15].

The current conventions in diagnosing a comorbid psychiatric disorder and a substance-use disorder are as follows:

1. Do not list "substance-induced psychosis" or "substance-induced mood disorder" as additional diagnoses when the substance use exacerbates the symptoms of an already established psychiatric disorder. Only list the substance-use disorder and the psychiatric disorder that was worsened.
2. Examine and contrast the onset of psychiatric symptoms with the beginning of substance use, as well as examining whether symptoms seem to persist to a robust degree even when the patient is abstinent from the substance, in determining whether to attribute a psychiatric syndrome to the substance use.
3. Most substances of abuse are associated with syndromes that persist even with prolonged abstinence.

Medical Comorbidity

Chronic drug and alcohol use significantly increases the likelihood that a person will use an ED for medical treatment [16]. Chronic substance use has deleterious effects on the general health of drug users. For example, injection heroin users are more vulnerable to HIV, hepatitis B and C, abscess formation at injection sites, avascular necrosis of the bone, endocarditis, and renal insufficiency. Cocaine use is associated with stroke, acute myocardial infarction, dysrhythmias, aortic dissection, seizures, and respiratory problems. Methamphetamine use is associated with acute renal failure due to rhabdomyolysis.

Service Utilization

Substance-use disorders are highly prevalent among patients presenting in the ED. The 2007 Nationwide Emergency Department Sample (NEDS) shows that 12.5% of all ED visits involved diagnoses related to mental health and substance-use disorders. Of all mental health and substance-use disorders (SUDs), 64% were for mental health disorders alone, 24% were for substance-use disorders alone, and 12% were for co-occurring disorders [2]. Between 2006 and 2013, the population rate of ED visits involving SUDs increased by 37% [17].

Unintentional poisoning from opiate prescription drugs is a rising problem. According to the CDC, opioid overdose deaths in the US have quadrupled from 8050 in 1999 to 33,091 in 2015. The deaths were initially driven by prescription opioid misuse and more recently by heroin and other illicit opioid use. In the period from 2010 to 2015, heroin overdose deaths also quadrupled from 3036 to 12,989. A sharp increase in the supply of heroin and illicitly manufactured fentanyl is considered to be contributing to increased deaths [18] (see more in ref. [28, 29, 30]).

Brief Interventions

The ED provides a unique opportunity to engage patients about their drug use. Clinical reports for screening, brief intervention, and referral to treatment (SBIRT) instituted by SAMHSA in the EDs across the US initially reported a reduction in illicit drug and alcohol abuse 12 months after the screening [19]. However, a recently published benefit–cost analysis indicates that this intervention did not result in any significant impact on total economic benefit from SBIRT [20].

Drugs of Abuse and Intoxication

Alcohol Prevalence and Community Impact

Alcohol intoxication is the most prevalent of the substance intoxications encountered in the ED. The estimated total number of ED visits attributable to alcohol from 1992 through 2000 was 68.6 million (65.6–71.7 million), which averages to 7.6 million alcohol-related ED visits per year. Alcohol-related visits accounted for 8% of the total 866.5 million ED visits from 1992 through 2000 [21].

According to the CDC's Alcohol-Related Disease Impact (ARDI) tool for 2006–2010,

excessive drinking led annually to 88,000 deaths and 2.5 million years of life lost [22]. Excessive alcohol use is accounted for 1 in 10 deaths among working-age adults in the United States [23].

Alcohol is highly prevalent among individuals with mood and anxiety disorders. According to the results from the National Epidemiological Survey on Alcohol and Related Disorders, of individuals who presented to treatment for alcohol use disorder, 41% had independent (comorbid) mood disorder, and 33% had an independent anxiety disorder. The authors of this study argue that treatment for a mood or anxiety disorder should not be withheld from those with alcohol or drug use in stable remission on the assumption that most of these disorders are due to intoxication or withdrawal [24].

Binge drinking (defined as intake of at least five drinks on one occasion for men and at least four drinks on one occasion for women) and heavy drinking (defined as daily intake of more than two drinks for men and more than one drink for women) are considered excessive drinking [23]. Binge drinking, the most common form of excessive alcohol consumption, usually results in acute intoxication and is responsible for over half of the deaths and three-quarters of the economic costs of excessive drinking. Binge drinking can be harmful without the drinker being alcohol-dependent. In fact, the majority of binge drinkers are not alcohol-dependent.

Compared with patients presenting to primary care settings, ED patients are more likely to be drinking alcohol to an excessive and harmful level [25]. Underage drinking (ages 12–20) is a significant factor in ED visits: Between 2010 and 2013, an estimated 656,827 alcohol-misuse-related ED visits were made by patients aged 12–20. Alcohol-only visits accounted for 80% of all underage alcohol-misuse-related visits [26].

Management

When a patient presents with suspected alcohol intoxication as part of the clinical presentation, it makes sense to check the BAL (blood alcohol level) early in the evaluation process. If the patient refuses a blood draw, a urine alcohol level is a less accurate but modestly useful method of estimating blood alcohol. The breath alcohol level appears to be less reliable as serum blood alcohol increases, so it is probably unsuitable for ED use [27]. It is essential to ask the patient when he or she last drank. A person who drank a significant amount just before entering the ED may have sequestered alcohol in the stomach, and the BAL will continue to rise as he or she absorbs the bolus. It is also important to ask the patient about any illicit drug use and how recently the substance was used. Note that a highly tolerant individual can appear only modestly impaired at a BAL that would render an alcohol-naïve individual unconscious.

Blood alcohol levels will decline at a rate determined by such factors as liver volume, liver health, ethnicity, gender, and patient tolerance to alcohol. Nontolerant individuals metabolize more slowly than alcohol-tolerant individuals, and women metabolize more slowly than men if their level of tolerance is equal. Individuals with the impaired hepatic function will metabolize more slowly. A rate of 0.015–0.02 g/dL per hour is a fair estimate overall of nontolerant individuals' capacity for metabolizing alcohol. A tolerant individual may metabolize at a rate closer to 0.04 g/dL per hour. Knowing the likely rate, one can estimate how long it will take before the patient is ready to be seen for a mental health interview. Emergency physicians and psychiatrists take varying approaches to the timing of a mental health interview for the patient intoxicated with alcohol. No single standard exists, but the patient should, at a minimum, be clinically assessable. Some follow more objective BAL cutoffs that correlate with established legal limits for driving, which vary by state. In some instances (e.g., for legal purposes), a BAL of 0 may be needed before the interview is completed.

Intoxicated patients may be brought to the ED for assessment after expressing suicidal or homicidal impulses and intent, causing a disturbance in the community, or having been found in a state of unconsciousness. The mental health exam should be completed once the patient is decisional. Suicidal or homicidal ideation may be dis-

avowed once the patient is sober. If the patient continues to endorse suicidal or homicidal ideation after sobering, the patient should be assessed and managed accordingly.

Physical findings in the chronically overdrinking individual include conjunctival injection, abnormal skin vascularization evident on face and neck, tongue tremor, hand tremor, and hepatomegaly. Laboratory findings may consist of high mean red cell volume (MCV) on the complete blood count, elevated serum aspartate aminotransferase (AST), and elevated serum gamma-glutamyl transferase (GGT). The serum carbohydrate-deficient transferrin (CDT) assay is also sensitive to heavy drinking and is not affected by the comorbid liver disease.

If the patient shows up-gaze paresis, along with confusion, one should be concerned mainly with acute thiamine-deficiency-associated Wernicke's encephalopathy. In such a situation, thiamine should be administered immediately (100 mg IV or IM) and supplemented daily with oral 100-mg doses for at least 3 days. One needs to keep in mind that high utilizers of the ED services due to alcohol intoxication may end up receiving multiple doses of thiamine and exhibit signs of thiamine intoxication, such as dysrhythmia, hypotension, headache, weakness, and seizures.

One should also keep in mind the possibility for an alcohol-intoxicated patient to have suffered a traumatic brain injury, typically from falling, before arriving at the ED. The resulting confusion could be mistaken for simple intoxication. Alcoholic psychosis may recur during subsequent episodes of alcohol intoxication. If the patient experiences a subacute or chronic psychosis, management with antipsychotic medication is indicated. The assessment and management of alcohol withdrawal state in the ED are covered elsewhere in this text.

The ED is a critical platform for engaging alcohol-affected patients. Patients should be offered follow-up in the community, including non-hospital-based detoxification, though in most states these resources are limited. As noted above, the SBIRT program has shown limited cost impact.

Opioids

Unless opioid intoxication occurs in the context of accidental or intentional overdose, patients rarely come to the ED in a state of opioid intoxication per se. Opioid abusers, however, are more likely to seek ED services in the state of opioid withdrawal. Individuals who abuse opioids receive medical attention because of medical complications of drug use, withdrawal, or overdose. Opioid intoxication is suspected when a patient has pupillary constriction and symptoms of slurred speech, drowsiness, and impaired attention and memory. Opioid overdose is a medical emergency, and patients with the triad of classic symptoms (pinpoint pupils, respiratory depression, and altered sensorium/coma) warrant emergency administration of naloxone, which can be administered intravenously, intramuscularly, or subcutaneously. The usual initial dose is 0.4–2 mg. If the desired degree of counteraction and improvement in respiratory function is not obtained, it may be repeated at 2–3-minute intervals. One should be cautioned that abrupt reversal can result in elevated blood pressure, tachycardia, tremulousness, seizure, and, in rare events, cardiac arrest. Opioid withdrawal, in contrast, is rarely fatal, but the comfort of the patient may be helped by the appropriate use of an opiate withdrawal regimen.

Prescription opiate use has become increasingly prevalent among patients presenting in EDs, and the most commonly abused drugs include hydromorphone (Dilaudid), hydrocodone (in Vicodin/Norco), oxycodone (Oxycontin and in Percocet), and oxymorphone (Opana), though methadone also is commonly abused. In recent years, two opioid trends have emerged that are particularly menacing: (1) increasingly prevalent fentanyl and fentanyl analogs flooding the drug market from illicit sources and leading to what is termed an epidemic of opioid-related overdose deaths [28, 29] and (2) the appearance of an array of synthetic opioids, such as U-47700, nicknamed "Pink" [30]. Additionally, a potent opioid, carfentanil, is appearing in some street mixtures with heroin and other drugs. This is a drug used for sedation or general anesthesia in large ani-

mals, such as elephants, and is not meant for human use [31]. In the last several years, especially after the FDA approval of naloxone intranasal spray for reversal of heroin overdose in 2015, EDs across the country have been distributing naloxone to patients identified at risk for opioid overdose [32]. There is an increasing awareness that the distribution of naloxone kits to laypersons who might witness an opioid overdose can help reduce opioid overdose mortality [33]. This action undoubtedly is a complex matter raising some controversies, including a concern that readily available naltrexone for laypersons may increase opiate addiction [34]. Additionally, ED-initiated buprenorphine for opioid dependence with continuation in primary care was found to increase engagement in addiction treatment and reduce illicit opioid use at 30 days, compared to referral only or a brief intervention with referral [35]. A subsequent study replicated the short-term benefit of ED-initiated buprenorphine at 2 months but showed no difference in addiction treatment engagement at 6 and 12 months [36].

Sedative-Hypnotics

Benzodiazepines

Benzodiazepines are sedative, hypnotic, and anxiolytic agents that are typically referred to by drug uses as "downers." According to the Drug Abuse Warning Network (DAWN) report, drug-related ED visits involving benzodiazepines increased by 124% from 2004 to 2011, and alprazolam (Xanax) and clonazepam (Klonopin) were the most frequently reported as the drugs of abuse [1]. While opioids are most often associated with accidental overdose, benzodiazepines are the most commonly ingested prescription medications in suicide attempts. The symptoms of benzodiazepine intoxication are similar to alcohol intoxication, and they include an altered level of consciousness, drowsiness, confusion, impaired judgment, slow and slurred speech, incoordination, and ataxia. Severe intoxication/overdose can lead to coma, respiratory depression, and death. Benzodiazepine overdose patients are typically managed in EDs with supportive care such as maintenance of adequate ventilation and hydration. In contrast to the role in iatrogenic oversedation, caution is advised regarding the utility of flumazenil, the benzodiazepine antidote, in a chronic user, as it may precipitate severe withdrawal symptoms, including seizures.

Of particular concern is when benzodiazepines are used in combination with substances like opioid pain relievers or alcohol. According to the DAWN report, over a 7-year period (2005–2011), 32% of hospital emergency department visits involving benzodiazepines resulted in severe medical outcomes such as hospitalization (or in rare cases, death). The risk of a severe outcome was 44% for the visits involving the use of benzodiazepines in combination with opioid pain relievers. Similarly, 44% of ED visits associated with the combined use of benzodiazepines and alcohol resulted in serious adverse medical outcomes [37]. Benzodiazepine withdrawal is a serious medical emergency due to the risk of seizures, peripheral nervous system and electrolyte instability (due to profuse diaphoresis), and acute anxiety syndrome with restlessness and insomnia. Patients with acute anxiety due to benzodiazepine withdrawal are often seen and managed in the psychiatric emergency service.

Barbiturates

Barbiturates are used to treat various seizure disorders. They are classified based on their duration of action: ultra-short-acting, short-acting, intermediate-acting, and long-acting. Barbiturate intoxication causes central nervous system (CNS) depression symptoms that are similar to alcohol and benzodiazepine intoxication, including nystagmus, vertigo, slurred speech, lethargy, confusion, ataxia, and respiratory depression. Severe overdose may result in coma, shock, apnea, and hypothermia. In combination with alcohol or other CNS depressants, barbiturates have additive CNS and respiratory depression effects.

Barbiturate withdrawal is life-threatening, with signs and symptoms developing within

24 hours. Patients may present to the ED with insomnia, restlessness, and severe anxiety.

Gamma-Hydroxybutyrate (GHB)

GHB is known as a dietary supplement that gained popularity as a club drug in the late 1990s and early 2000s. Sporadically, GHB is a drug of abuse leading to an ED visit. GHB, also referred to as "liquid ecstasy," is a potent CNS depressant, and the effects of intoxication are a profound alteration of mental status and respiratory depression, with periods of apnea. Deaths have been reported with severe GHB intoxication [38]. GHB discontinuation can lead to a significant withdrawal syndrome that is similar to sedative-hypnotic and alcohol withdrawal. With appropriate management, most patients fully recover within 6 hours. Nevertheless, the challenge lies in the recognition and detection of GHB, because routine toxicology screening does not detect this substance [39].

Stimulants

Cocaine

As noted above, cocaine is the most common illegal substance that leads to ED visits, which in 2011 accounted for 162 visits per 100,000 [1]. Cocaine is a stimulant with powerful effects on the central and peripheral nervous system that acts by blocking the reuptake of dopamine, norepinephrine, and serotonin. It also modulates the endogenous opiate system. Cocaine intoxication leads to some physical signs and symptoms, such as hypertension, tachycardia, chest pain, myocardial infarction (MI), mydriasis, diaphoresis, delirium, stroke, and seizures. Acute cocaine intoxication may present with anxiety; agitation; paranoia; hallucinations; feelings of increased energy, alertness, and intense euphoria; and decreased tiredness, appetite, and sleep.

Cocaine may be smoked (crack-cocaine), insufflated (snorted), injected, and orally ingested (cocaine salt). The onset, peak, and duration of cocaine's effects vary depending on the route of administration. The fastest absorption and the peak effect are after inhalation. Repeated cocaine users may use it as frequently as every 10 minutes, may binge with it for as long as 7 days, and may use as much as 10 grams per day.

Chest pain due to cardiac ischemia is the most frequent cocaine-related medical event for which patients seek treatment in inner-city EDs [40]. The most frequently occurring cardiac complications of cocaine are syncope, angina pectoris, and MI. In some instances, the outcome is acute cardiac death. The typical patient with cardiac-related MI is a young man without cardiovascular risk factors other than smoking. The relative risk of MI is elevated 24 times within 60 minutes after cocaine use, and the incidence of MI is about 6% [41]. There have been recent reports of fever and severe agranulocytosis associated with cocaine that had been adulterated with levamisole [42].

Psychiatric symptoms are prominent in cocaine intoxication and account for about 30% of cocaine-related presentations, compared to 16% and 17% for cardiopulmonary and neurologic symptoms, respectively. Suicidal intent was the most common psychiatric reason for presentation [43]. Psychiatric manifestations of cocaine intoxication include anxiety, agitation, euphoria, and intense paranoia. Because of overlapping psychiatric manifestations of cocaine intoxication and bipolar mania, differentiation between the two can be challenging in the ED. One should keep in mind the following: SUD are commonly comorbid in patients with bipolar affective disorder, and substance abuse often is a manifestation of the core criteria of mania, specifically excessive involvement in activities with a high potential for painful consequences. Manic episodes can frequently be triggered by insomnia due to stimulant abuse. These factors are often exacerbated by the elevated rates of noncompliance with medication in patients abusing substances, which in turn render patients vulnerable to decompensation [44].

Depression and suicidal thoughts often accompany acute cocaine withdrawal. Excessive tearfulness has been described as a distinct sign of cocaine-induced depression in patients pre-

senting in a busy urban PES [45]. A typical patient with cocaine-related psychiatric symptoms presents to the ED in the early morning hours after a binge in a state of high adrenergic dysregulation, dysphoric and suicidal, with injected conjunctiva, asking for food and promptly falling asleep. Disposition of such patients may be a challenge due to their suicidality [44]. The treatment of cocaine intoxication is determined by the presenting symptoms. Chest pain warrants a medical workup for cardiovascular complications. Such patients often receive hydration and benzodiazepine or other sedating agents to reduce anxiety and blunt surges in blood pressure and heart rate. It is worth noting that beta-blockers should be avoided in cocaine-associated MI because of theoretical concerns of unopposed alpha-adrenergic stimulation. In patients who are severely agitated or intensely paranoid, treatment with oral or intramuscular antipsychotic medication may be indicated.

Methamphetamine

In the early 2000s, there was a nationwide methamphetamine epidemic. In some localities, ED visits involving methamphetamine declined by 2006. However, since 2007 the rates of methamphetamine have increased again. According to DAWN 2011 report, ED visits involving methamphetamine accounted for 4% of all drug-related ED visits [46]. The majority (62%) of these ED visits involved other drugs. Injecting methamphetamine along with heroin ("methball") has risen rapidly in some localities, as noted in Denver in a recent epidemiological study [47].

Like cocaine, methamphetamine exerts powerful stimulant effects on the brain, but the results last longer than after cocaine use, giving rise to more noticeable medical and psychiatric symptoms. Methamphetamine intoxication can lead to serious medical consequences, including hypertension, arrhythmias, MI, stroke, acute renal failure due to rhabdomyolysis, seizure, delirium, and death. People who inject methamphetamine are at increased risk of contracting infectious diseases such as HIV and hepatitis B and C. Methamphetamine use can also alter judgment and decision-making, leading to risky behaviors such as unprotected sex, which also increases the risk for sexually transmitted infection. Psychiatric consequences include psychosis, mania-like symptoms, severe agitation, and violence. Psychosis is the most common presenting symptom (80%) in methamphetamine-intoxicated patients who are seen in PES. These patients were most often Caucasians (75%) referred by police with an extended duration of stay in the ED [48]. By clinical observation, patients most often present in a state that has been described by the term "tweaking," which involves a state of high arousal, agitation, and uncontrollable movements, with prominent dysphoria, hallucinations, and paranoia (Table 5.1).

Due to their extreme agitation, patients with methamphetamine intoxication are often treated with sedating agents (benzodiazepines), alone or in combination with antipsychotic agents. There are regional differences that dictate the utilization of physical restraints and involuntary administration of medications in methamphetamine-intoxicated patients. However, it is essential to keep in mind that such patients are highly distressed and are likely to accept medications voluntarily, mainly if the medication is offered in a rapidly dissolvable form [48]. As in treating cocaine-intoxicated patients in the ED, methamphetamine-intoxicated patients may need

Table 5.1 Methamphetamine: effects and duration of euphoria by route of administration

Route	Onset	Peak effect (min)	Duration (hrs)
Smoking	Within seconds	1–5	20
Snorting	Within seconds	3–5	12
Intravenous	Within seconds	1–3	12
Oral	10 min	15–20	12

intravenous rehydration to correct electrolyte imbalance and acute renal insufficiency.

MDMA (3,4-Methylenedioxymetham phetamine)

MDMA—also known as "Ecstasy" or, more recently, "Molly"—is similar to both the stimulant amphetamine and the hallucinogen mescaline. Ecstasy is known as a club drug, and typically, it is used by young individuals in parties, raves, and clubs. Ecstasy/Molly is a powerful indirect releaser of serotonin and a moderate releaser of dopamine. Regarded by most users as a harmless substance, the acute effects of MDMA intoxication are an increase in energy and a sense of empathy. Its psychiatric effects include blunting of the senses, confusion, lack of judgment, depression, anxiety, anger, paranoia, hallucinations, and aggression.

Ecstasy intoxication can lead to serious medical complications such as hypertension, tachycardia, rhabdomyolysis with acute renal failure, and hyperthermia. One should keep in mind that some MDMA users believe that they can avoid hyperthermia by drinking large amounts of water, which puts them at risk of hyponatremia from diuresis and marked increase in free water intake.

Ecstasy users may present in a hyperactive delirious state. Molly—slang for "molecular"—refers to the pure crystal powder form of MDMA. Usually purchased in capsules, Molly has become more popular in the past few years. Users may be seeking out Molly to avoid the additives, such as caffeine, methamphetamine, and other harmful substances that are commonly found in in Ecstasy pills. News stories have reported Molly capsules containing harmful substances that include synthetic cathinones. The effects of Molly can last from 3 to 6 hours [49]. ED staff must be alert to addressing serotonin syndrome, which can be precipitated by the patient's concurrent use of stimulant drugs. Most standard urine drug screen tests have low sensitivity for MDMA, so the Ecstasy level needs to be quite high to show a positive test.

"Bath Salts"

Recently, there has been increased attention to a new generation of designer drugs, the so-called "bath salts." The Drug Abuse Warning Network (DAWN) first detected a measurable number of emergency department (ED) visits involving bath salts in 2011 [50]. Bath salts were named in 22,904 visits, or about 1% of all drug-related ED visits. One-third of these visits involved bath salts only, and two-thirds involved other drugs.

Bath salt products were sold legally online as "legal highs" under a variety of names such as "Ivory Wave," "White Lightning," and "Vanilla Sky," but in 2011, the Drug Enforcement Agency (DEA) declared bath salts to be a controlled substance. The use of such products has led to an increasing number of ED visits and overdoses throughout the country. These products contain amphetamine-like substances such as methylenedioxypyrovalerone, mephedrone, and methylone [51]. However, to keep ahead of the game with the law, bath salt developers are persistently coming up with new substitute compounds [52]. These drugs are chemically similar to amphetamines, cocaine, and MDMA, and the effects are more potent to the brain. Ingesting or snorting bath salts can cause arrhythmias, chest pain, MI, hypertension, hyperthermia, seizure, stroke, aggressive and violent behavior, hallucinations, paranoia and delusions, excited delirium, and, in extreme cases, death. Bath salts are rapidly absorbed after oral ingestion, with intoxication peaking at 1.5 hours and lasting for 3–4 hours. Patients who are intoxicated on bath salts may require physical restraints and high doses of sedatives because of the risk of harming themselves or others. Treatment includes hydration to address emerging rhabdomyolysis and benzodiazepines to control seizures [53].

ADHD Stimulant Medications

Several CNS stimulants are used for the treatment of the attention-deficit/hyperactivity disorder (ADHD), including methylphenidate (e.g., Ritalin, Concerta), amphetamine-

dextroamphetamine (e.g., Adderall), dexmethylphenidate (e.g., Focalin), and dextroamphetamine (e.g., Dexedrine). ADHD stimulant medications can also be misused to suppress appetite, enhance alertness, or cause feelings of euphoria. The primary abusers are young individuals (<25 years of age) who obtain the drug from a friend or a classmate. Other abusers may purchase it from a fraudulent prescription or by doctor shopping. According to DAWN, the number of ED visits involving ADHD stimulant medications increased between 2005 and 2010 from 13,379 to 31,244 visits [54]. The number of ED visits involving ADHD stimulant medications increased significantly for adults aged 18 or older. Acute intoxication with a substance such as methylphenidate results in symptoms similar to those seen with cocaine, including euphoria, delirium, confusion, paranoia, and hallucinations. Additional symptoms may include extreme anger, threats, or aggressive behavior.

Hallucinogens and Dissociative Agents

Phencyclidine (PCP)

Since phencyclidine entered the market in 1957 as a dissociative anesthetic, it has become a significant drug of abuse, due to its psychotropic effects. The estimated number of PCP-related ED visits increased more than 400% between 2005 and 2011 (from 14,825 to 75,538 visits). The most substantial increase in PCP-related ED visits was seen among patients aged 25–34. It is smoked (usually in a mix with marijuana) or, less often, ingested orally. Low doses cause an acute confusional state with excited delirium lasting several hours; stimulant effects predominate. More massive doses cause nystagmus, muscle rigidity, ataxia, stereotyped movements, hypertension, hypersalivation, sweating, amnesia, and an agitated psychosis. The psychotic state induced by phencyclidine is so similar to that of schizophrenia that intermittent administration of phencyclidine has become a standard pharmacological model for schizophrenia in the laboratory. The increase in ED visits involving PCP is of particular concern because it is reputed to be the most dangerous among hallucinogens for causing violent behavior [55].

Unfortunately, PCP is relatively easy and inexpensive to manufacture illicitly. Marijuana has replaced alcohol as the most common secondary substance of abuse in phencyclidine abusers who present for medical attention.

The PCP user is managed conservatively in the ED by keeping the patient physically safe and providing reduced stimulation. An early check for emerging rhabdomyolysis is advisable, and hydration should be maintained.

Ketamine

Ketamine—or the street-named "K," "Special K," "KitKat," or "Vitamin K"—is a powerful dissociative anesthetic that produces similar effects to phencyclidine but with a shorter duration. The common presenting complaints include prominent anxiety, chest pain, and palpitations, and typical findings include confusion, amnesia, mydriasis, bidirectional nystagmus, tachycardia, rigidity, seizures, and usually short-lived hallucinations. The most common complication of ketamine intoxication is severe agitation and rhabdomyolysis. Symptoms are typically short-lived, and patients most often are discharged within 5 hours of presentation [56]. Ketamine intoxication is managed with benzodiazepines to mitigate the anxiety and agitation. Lorazepam, 1–2 mg orally or IV, is the mainstay of treatment. Of note, in recent years, ketamine IM has been used by emergency medical response teams across the country for prehospital sedation of violent and agitated patients and excited delirium [57].

Lysergic Acid (LSD)

LSD is not a standard drug of abuse. However, its damage is prevalent among high school students. According to the DAWN 2011 report, there were 4819 LSD-related visits. These visits were pri-

marily made by young individuals, aged 18–24 [1].

Typically, it is ingested in pill form or dissolved on a piece of paper. The signs and symptoms of intoxication develop within an hour after ingestion and include tachycardia, hypertension, hyperthermia, dilated pupils, distorted perception of time, and depersonalization. LSD is associated with the unique sensory misperception called "synesthesia," whereby colors are heard and noises are seen. These symptoms usually clear 8–12 hours after ingestion, though feelings of numbness may last for several days [58].

ED presentations typically include manifestations of intense anxiety, such as a panic attack ("bad trip"), and can be managed with reassurance and, in some instances, lorazepam or diazepam. Other presenting symptoms include delirium with hallucinations, delusions, and paranoia. Occasionally, a patient may present to the ED with ongoing psychotic symptoms, long after the drug was eliminated from the system, or with the spontaneous recurrence of drug effects, known as "flashbacks." While death from an overdose of LSD is rare, ingestion of high doses carries a significantly higher risk of death due to convulsions, hyperthermia, and cardiovascular collapse.

Phenethylamines (such as mescaline from the peyote cactus, 2C synthetic products (2C-I ("Smiles"), 2C-B ("Nexus"), 2C-E, and 2C-T-7 ("7-up," "Blue Mystic")), psilocybin/psilocin (the psychoactive ingredient in psilocybin mushrooms), and Salvia divinorum) are also hallucinogens. The frequency of use is not well known, since ED visits for intoxication are uncommon. The effects of intoxication are similar to LSD [59].

Dextromethorphan

Dextromethorphan (DXM) is a cough suppressant that is found in many over-the-counter cough and cold preparations, such as Coricidin, Nyquil, and Robitussin. Some popular street names for DXM include "Tripple C," "Candy," "Dex," "Robo," "Rojo," and "Tussin." According to DAWN reports, DXM accounts for about 1% of all drug-related ED visits. However, the significance of DXM misuse is that 50% of such ED visits are made by youth, aged 12–20 years. Structurally related to the opiate receptor antagonist codeine, its metabolite dextrorphan exhibits serotonergic activity and inhibits NMDA receptors. Its unique mechanism of action results in psychotropic effects that are similar to ketamine and phencyclidine. Neurobehavioral effects of DXM typically begin from 30 to 60 minutes after the ingestion and may persist for up to 6 hours. DXM intoxication leads to a combination of euphoric, stimulant dissociative, and sedative effects, and neurological signs such as ataxia, dystonia mydriasis, nystagmus, and coma. It also causes nausea and vomiting, diaphoresis, hypertension, tachycardia, and respiratory depression. In rare instances, DXM has been associated with the development of serotonin syndrome. To address these dangers, the American Association of Poison Control Centers has developed practice guidelines for the management of DXM poisoning/intoxication [60].

Inhalants

Inhalants and inhalant use disorders recently were the subject of a comprehensive review by Howard et al. [61]. Inhalants are substances that produce a psychoactive effect when their vapors are inhaled, and are rarely abused by any other means. These substances include aerosols (containing propellants and solvents), gases (e.g., nitrous oxide), volatile solvents (liquids that vaporize at room temperatures, such as correction fluid, paint thinner, dry-cleaning fluids, and glues), and nitrites. Everyday household products often are a source for the first three types of inhalants. This makes the inhalants a particular problem among early- to mid-adolescents, who may not have easy access to other substances of abuse [62]. The first three types of inhalants act directly on the central nervous system.

The fourth type of inhalant, the nitrites (e.g., amyl nitrite, isobutyl nitrite), are abused by adults

and older teens, for the most part, with a goal of enhancing the sexual experience. Unlike the first three types of inhalant, nitrites relax the muscle and dilate blood vessels. Known as "poppers" or "snappers," abuse of nitrites is linked to unsafe sexual practices, increasing the risk of contracting and spreading hepatitis and HIV.

Inhalants enter the bloodstream rapidly and produce intoxication effects within seconds of inhalation. The short-term effects may include initial euphoria, dizziness, impaired coordination, slurred speech, loss of inhibition, hallucinations, and delusions. Users often deal with the short duration of intoxication by repeatedly inhaling, which can lead to a decreased level of consciousness and death. After repetitive use within the span of a few minutes, an inhalant user may be drowsy for several hours. A headache often accompanies repetitive inhalation. Many common inhalants (butane, propane, Freon, trichloroethylene, amyl nitrite, butyl nitrite) are linked to "sudden sniffing death syndrome." Chronic abuse of volatile solvents can lead to demyelination and clinical syndromes resembling multiple sclerosis. Such neurologic functions as movement, vision, hearing, and cognition can be affected. In the worst cases, dementia is the result. Hepatotoxicity, cardiomyopathy, impaired immune function, and lung and kidney damage all can result from inhalant abuse. In earlier stages, such a loss may be partially or even wholly reversible. There are concerns about prenatal exposure to inhalants as well [63].

Cannabinoids

The increasing medicalization of marijuana has thrown a new wrinkle into our understanding of the costs and benefits of marijuana use. It has been described that medicalization typically for severe pain or severe nausea and vomiting associated with chemotherapy often encourages regular use [64]. Such steady use can tip the balance so that what might have been a relatively minor contributor to psychiatric problems becomes more substantial. In some patients, for example, increased marijuana use can be associated with increased impulsivity and suicidality, with or without a preexisting depression [65].

The acute effects of marijuana intoxication, such as sedation, failure to consolidate short-term memory, altered sense of time, perceptual changes, decreased coordination, and impaired executive functioning, are commonly seen. There is substantial evidence that patients with schizophrenia who use cannabis experience a more severe course of illness [66]. Patients with recent-onset psychosis who use cannabis regularly have more severe psychotic symptoms and more cognitive disorganization than comparable patients who do not use cannabis [67].

Cannabis dependence is associated with physiological tolerance and a physiological withdrawal syndrome. Symptoms may appear as early as a day after discontinuation and last 1–3 weeks. Withdrawal symptoms include craving, irritability, anger, dysphoric mood, restlessness, insomnia, and diminished appetite. Treatment relies on psychosocial therapies such as motivational interviewing, specific cognitive-behavioral therapy, and contingency management.

Synthetic Cannabinoids

Further complicating our understanding of cannabinoids in the ED, synthetic cannabinoids (e.g., "Spice" products or "K2") are a rapidly emerging class of drugs of abuse [66]. They are chemically similar to marijuana and sometimes are misleadingly called "synthetic marijuana" (or "fake weed"). They are often marketed as safe and legal. Because they act as a full agonist to the THC receptors, they may affect the brain much more powerfully than marijuana.

It was estimated that in 2011 there were 28,531 ED visits related to synthetic cannabinoids [69]. The harmful effects of these products were first reported in the US in 2009. Since then, the drugs have spread throughout the country. Poison centers received 2668 calls about expo-

Table 5.2 Adverse clinical effects of synthetic cannabinoids

Central nervous system	Seizures Agitation Irritability Loss of consciousness Anxiety Confusion Paranoia
Cardiovascular	Tachycardia Hypertension Chest pain Cardiac ischemia
Metabolic	Hypokalemia Hyperglycemia
Gastrointestinal	Nausea Vomiting
Autonomic	Fever Mydriasis
Other	Conjunctivitis

From Seely et al. [68]

sures to these drugs in 2013; 3682 exposures in 2014; and 7794 exposures in 2015 [70]. Adverse effects reported with these synthetic cannabinoids are listed in Table 5.2. To date, at least 10 different plant species are being used in the manufacture of these substances, and the potency, duration of action, and potential for unexpected toxicity are variable as well. These products will not show up on current urine toxicological screens.

Conclusion

Drug intoxication is commonly involved in ED visits, and patients may present with a variety of medical and psychiatric complaints. Drug intoxication complicates clinical presentation and can lead to prolonged ED length-of-stay and deployment of resources (including the use of restraints in severe intoxication syndromes), and creates a challenge for disposition and treatment. Clinicians who work in the ED setting, including nursing staff, social workers, emergency medicine physicians, and psychiatrists, should be familiar with the toxidromes of the conventional drugs of abuse in order to: (1) make an appropriate diagnosis, (2) provide emergency management, including proper psychiatric and substance-use assessment and administration of medications, (3) refer to a short-term treatment that may include detoxification or admission into the hospital, or (4) relate to a longer term treatment in the community.

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