Chapter 2
Pharmacology of Commonly Abused Drugs

Abstract Various drugs are abused and workplace drug testing depending on the half-life of the abused drug tests for the presence of either the abused drug or its metabolites. For example, benzoylecgonine, a major metabolite of cocaine, is tested in workplace drug testing because the half-life of cocaine is approximately 15 min. Understanding the pharmacology of various abused drugs is essential in order to interpret test results in workplace drug testing. In addition to the federal mandate of five drugs, several other abused drugs are often tested for by private employers in workplace drug testing programs. The pharmacology of these abused drugs will be discussed in this chapter.

Keywords Amphetamine · Cocaine · Drug abuse · Marijuana · Opiate · Pharmacology

1 Introduction

Various drugs are commonly abused including amphetamine, methamphetamine, various benzodiazepines, barbiturates, cocaine, natural and synthetic opiates including methadone, phencyclidine, marijuana, propoxyphene, methaqualone and glutethimide. In addition, various designer drugs such as 3,4-methylenedioxyamphetamine, 3,4-methylene-dioxymethamphetamine and lysergic acid diethylamide (LSD) are also commonly abused. Many abused drugs have a half life and metabolites are often targeted for detection in the urine specimen during workplace drug testing. The pharmacology of abused drugs provides insight into the workplace drug testing.

2 Amphetamine, Methamphetamine and Related Drugs

Several stimulants and hallucinogens chemically related to phenylethylamine are referred to collectively as amphetamine-type stimulants. Amphetamines are sympathomimetic amines and are often optically active. In general, the D-enantiomers

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stimulate the central nervous system, while L-enantiomers act peripherally, for example provide appetite suppression. Although amphetamine was used in the past in treating depression, the current use of amphetamine and related compounds are limited to treating narcolepsy, attention deficit disorders, and minimal brain dysfunction. Amphetamines increase synaptic dopamine concentrations, primarily by stimulation of presynaptic release rather than by blockade of reuptake. Increased levels of dopamine in the brain elicit euphoria, contributing to the addictive properties of amphetamines. Amphetamines can be administered orally due to good bioavailability and the protein bindings of amphetamine and methamphetamine are low (less than 20%). Both amphetamine and methamphetamine are controlled substances and are classified as Schedule II drugs.

2.1 Metabolism of Amphetamine and Methamphetamine

Hepatic and renal clearance contribute to the elimination of amphetamine and methamphetamine with an elimination half-life between 6 and 12 h. Hepatic metabolism is extensive but a significant part of both drugs is excreted unchanged in urine. Amphetamine and related compounds are weak bases with pKa around 9.9 and they have relatively low molecular weights. Therefore, amphetamine and related compounds can diffuse through cell membranes and lipid layers to tissues and biological matrices which have pH lower than blood. In addition to urine and blood, amphetamine like compounds can also be detected in alternative matrices such as sweat, saliva, hair and nail [1].

A significant portion of both amphetamine and methamphetamine are excreted in the urine unchanged. Amphetamine also undergoes aromatic hydroxylation to para-hydroxyamphetamine and oxidative deamination to produce finally benzoic acid [2]. A part of methamphetamine is amphetamine. Major metabolites of amphetamine and methamphetamine are listed in Table 2.1. Chemical structures of amphetamine and methamphetamine are given in Fig. 2.1.

2.2 Designer Drugs Derived from Amphetamines

One of the most abused designer drugs which is also an analog of amphetamine is 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). This drug was synthesized by a chemist at Merck in 1914 as an appetite suppressant. Another closely related designer drug, 3,4-methylenedioxyamphetamine(MDA) was synthesized first in 1910. After 1986, a large number of amphetamine analogs were synthesized by clandestine laboratories to produce more potent effects after abuse. These designer drugs include para-methoxy-amphetamine (PMA), para-methoxy-methamphetamine (PMMA), 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA), 2,5-dimethoxy-4-methylamphetamine (DOM) and 2,5-dimethoxy-4-methylthioamphetamine (DOT) [1,2]. Other designer drugs in this class include 4-iodo-2,5-dimethoxyamphetamine (DOI), 2,5-dimethoxy-4-bromo-amphetamine

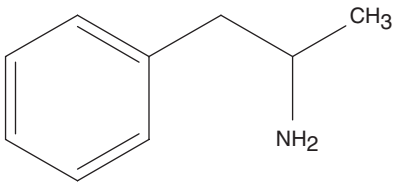
Table 2.1 Major metabolites of drugs of abuse

Drug	Major metabolite
Amphetamine	Unchanged drug
Methamphetamine	Amphetamine
Barbiturates	
Secobarbital	3-Hydroxysecobarbital
Pentobarbital	3-Hydroxy-pentobarbital
Amobarbital	3-Hydroxy-amobarbital
Phenobarbital	*p*-Hydroxy-phenobarbital[a]
Benzodiazepine	
Alprazolam	4-Hydroxy-alprazolam, α-hydroxy-alprazolam
Diazepam	Oxazepam[a], nor-diazepam
Lorazepam	Conjugated with glucuronic acid
Clonazepam	7-Aminoclonazepam
Triazolam	4-Hydroxy-triazolam α-hydroxy-triazolam
Cocaine	Benzoylecgonine, Ecgonine Methyl ester, Nor-cocaine
Opiates (*Natural and Synthetic*)	
Heroin	6-Monoacetylmorphine, morphine[a]
Codeine	Morphine, morphine-3-glucuronide
Morphine	Morphine-3-glucuronide
Hydrocodone	Hydromorphone
Oxycodone	Oxymorphone
Methadone	2-Ethylidene-1,5-dimethyl-3,3-diphenyl pyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrrolidine (EMDP)
Phencyclidine	*cis*- and *trans*-1-(1-phenyl-4-hydroxycy-clohexyl)piperidine,
Propoxyphene	Nor-propoxyphene
Tetrahydrocannabinol	11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol[a] (THC-COOH)

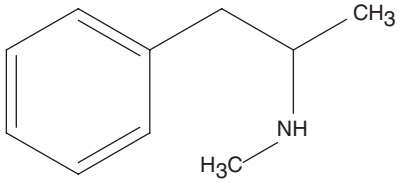
[a]Also excreted in urine as a conjugate of glucuronic acid

(DOB), 2,5-dimethoxy-4-bromo-methamphetamine (MDOB), *N*-methyl-1- [3,4]-methylenedioxy-phenyl)-2-butanamine (MBDB) and 3,4-(methylenedioxyphenyl)-2-butanamine (BDB). In addition, a chlorinated analog of MDMA has been detected in the urine of a drug abuser [3]. Bossong et al. also described two new ecstasy like substances; methylone (3,4-methylenedioxymethcathinone) and mCPPP (*meta*-chlorophenyl-piperazine). Methylone is the main ingredient of liquid designer drugs that appeared in the underground Dutch market [4]. The designer drugs such as PMA, PMMA and 4-methylthioamphetamine (4-MTA) have also been encountered at rave parties. 4-MTA is also sold as "ecstasy" or "flatliners" on the illegal drug market.

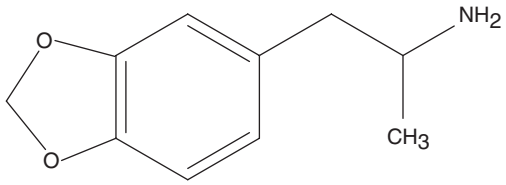
Other designer drugs derived from phenylethylamine include 4-bromo-2,5-diemthoxy-β-phenylethylamine (2C-B), 2,5-dimethoxy-4ethylthio-β-phenylethylamine (2C-T-2), 2,5-dimethoxy-4 propylthio-β-phenylethylamine (2C-T-7) and related drugs which are also abused. The drugs belonging to 2C series are among the most potent drugs and are selective to serotonin 5-HT_2 receptor. These drugs are also toxic and fatality from using 2C-T-7 has been reported. These designer drugs are mainly metabolized in the liver [5].



Amphetamine



Methamphetamine



3,4- Methylenedioxymethamphetamine

Fig. 2.1 Chemical structure of amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)

2.3 Metabolism of Designer Drugs Derived from Amphetamines

MDMA is metabolized to 3,4-methylenedioxyamphetamine(MDA) and a variety of other compounds including 4-hydroxy-3-methoxymethamphetamine (major metabolite), 3,4-dihydroxy-methamphetamine and 3-hydroxy-4-methoxymethamphetamine. The majority of 4-hydroxy-3-methoxymethamphetamine is excreted in urine as conjugated with glucuronide or sulfate. Polymorphism of CYP2D6 may partly regulate the O-demethylation pathway of MDMA metabolism and subjects deficient in CYP2D6 (poor metabolizers) may be at higher risk of developing MDMA toxicity. However, in this metabolic pathway, a mechanism based inhibition of enzyme is also encountered due to the formation of an enzyme-metabolite complex that affects all subjects regardless of genotype. Therefore

impact of CYP2D6 polymorphism on development of acute drug toxicity may be limited [6]. In contrast, CYP2D6 polymorphism plays an important role in the toxicity of the designer drug 4-methylthioamphetamine (4-MTA). The CYP2D6 rapid metabolizers may be at higher risk of developing from abuse of 4-MTA than the respective poor metabolizers [7].

2.4 Overdoses and Fatalities from Amphetamines and Related Drugs

Fatal poisoning from amphetamine and methamphetamine has been reported in the literature. In addition, methamphetamine abuse increases the length of hospital stay in minimally injured patients and results in trauma center resource utilization out of proportion to severity of injury [8]. Kojima et al. reported fatal methamphetamine poisoning in a 25-year-old woman who, after self-administration of 50 mg of methamphetamine hydrochloride, intravenously ingested approximately 1.5 g of methamphetamine after 3 h. Hyperpyrexia played an important role in her death with a rectal temperature of above 41°C estimated at death [9]. Ecstasy has been encountered in several fatalities in drug abusers. Byard et al. reported several fatalities from ecstasy abuse where hyperthermia (temperatures of 41.5–46.1°C) was the cause of three deaths. Other drugs involved in cases of severe toxicity/fatality included amphetamine/methamphetamine and PMA [10].

3 Barbiturates

Barbituric acid was first synthesized in 1864 and has no pharmacological activity but barbital derived from barbituric acid has sedative hypnotic property. Over 2,500 derivatives of barbituric acid were synthesized and approximately 50 of them have been marketed. Currently, there are approximately 12 different barbiturates which are used medically worldwide. Barbiturates are central nervous system depressants and are used medically as sedatives, hypnotics, anaesthetics as well as anticonvulsants. Based on the duration of action, barbiturates are classified as ultra short acting, short acting, intermediate acting and long acting barbiturates. Barbiturates can be administered both orally and intravenously.

The ultra-short acting barbiturates can produce anesthesia within minutes after intravenous administration. Currently thiopental and methohexital are commonly used drugs in this category. After oral administration, the short and intermediate acting barbiturates such as amobarbital, butalbital, butabarbital, pentobarbital, secobarbital and talbutal produce pharmacological action within 15–40 min and the effect may last up to 6 h. These drugs are used for treating insomnia and may also be used to achieve preoperative sedation. Long acting barbiturates such as phenobarbital and mephobarbital are classified as Schedule IV drugs and are medically used as anticonvulsants and also for day time sedation. The duration of action may last

up to 12 h. Usually short and intermediate acting barbiturates are abused and long acting barbiturates such as phenobarbital are rarely abused. Mechanism of action of barbiturates is GABA (gamma-amino butyric acid)-mediated inhibition of synaptic transmission. At low doses, barbiturates acts as modulators of GABA receptors enhancing postsynaptic inhibitory potential by activating chloride ion channel and at higher dosage barbiturates act as GABA agonists. Barbiturates demonstrate anxiolytic effects at a dosage close to producing hypnotic effects and such dosages also affect motor skill and mood. Chronic administration of barbiturates causes dependence. Because of nonselective binding of barbiturates with GABA receptors as well as negative side effects of barbiturates in treating anxiety disorder, these drugs are mostly replaced by benzodiazepines in treating anxiety disorder [11]. Depending on the abuse potential of barbiturates, they are classified either as a Schedule II or a Schedule III drug. Chemical structures of common barbiturates secobarbital, pentobarbital and phenobarbital are given in Fig. 2.2.

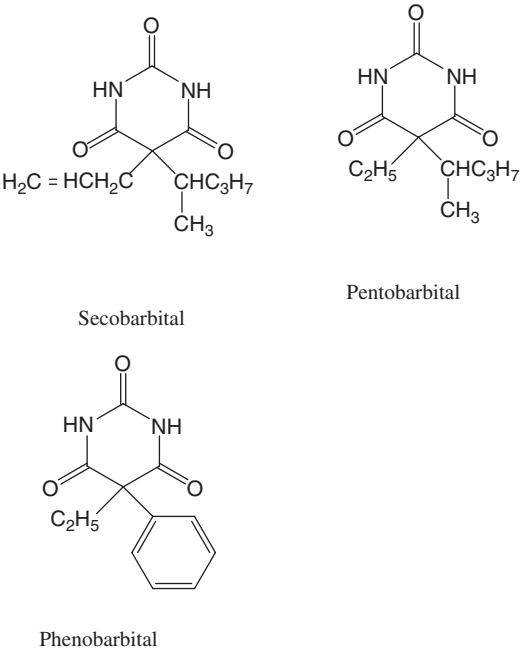


Fig. 2.2 Chemical structures of secobarbital, pentobarbital, and phenobarbital

3.1 Metabolism and Fatality from Barbiturates

Barbiturates are extensively metabolized to a number of different metabolites. Secobarbital is metabolized to 3-hydroxysecobarbital, secodiol and 5-(1-methylbutyl) barbituric acid. None of the metabolite has any pharmacological activity. Pentobarbital is metabolized primarily to 3-hydroxypentobarbital which

is inactive. Another metabolite, *N*-hydroxypentobarbital, is present in much lower amounts in urine compared to 3-hydroxypentobarbital. A major metabolite of amobarbital is 3-hydroxy-amobarbital, which has some pharmacological potency [12]. Major metabolites of commonly abused barbiturates are given in Table 2.1.

Pentobarbital is used in euthanasia of animals by veterinarians. Suicide by injecting veterinarian euthanasia agent containing pentobarbital has been reported [13]. There are other cases of suicide by taking pentobarbital [14]. Tracqui et al. described a fatal intoxication in a person involving secobarbital, nitrazepam and codeine. The blood concentration of secobarbital (11.48 μg/mL) was significantly higher (nitrazepam 1.72 μg/mL and codeine 0.036 μg/mL) than two other drugs and probably was the major cause of death [15].

4 Benzodiazepines

Benzodiazepines, as a class of drugs, are most widely prescribed drugs worldwide and are used for treating anxiety, insomnia, anesthetic adjuncts, anticonvulsants, muscle relaxant and for multiple other purposes. There are more than 50 different types of benzodiazepines but 15 members of this group are marketed in the United States and are classified as Schedule IV drugs. The most commonly prescribed benzodiazepines in the United States are diazepam, temazepam, alprazolam, lorazepam and clonazepam.

Benzodiazepines are positive modulators of the $GABA_A$ receptors and cause sedation, impaired memory and cognition, and loss of inhibition. These drugs may also cause increased agitation and insomnia, especially in pediatric and elderly populations. Benzodiazepines, like barbiturates, can be short acting or long acting. Short acting benzodiazepines are generally prescribed to treat insomnia. Long acting benzodiazepines are alprazolam, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, prazepam, and quazepam. These drugs are used for treating both insomnia and anxiety disorder while benzodiazepines such as clonazepam, diazepam, and clorazepate are also used as anticonvulsants. Long term treatment with benzodiazepines results in tolerance and dependence in the patient. Benzodiazepines have moderate potential for abuse and the most commonly abused benzodiazepines are alprazolam, diazepam, lorazepam, oxazepam, and triazolam. Chemical structures of commonly abused benzodiazepines are given in Fig. 2.3.

4.1 Pharmacology of Benzodiazepines

The half-life of benzodiazepines varies widely depending on the particular drug. Alprazolam has an average half-life of 12 h while average half-life of estazolam, flurazepam, quazepam, temazepam and zolpidem is 16, 1, 36, 11, 2.9 and 2.3 h respectively [16]. Benzodiazepines are extensively metabolized by liver enzymes and are excreted in the urine often as glucuronide conjugate. Oxazepam, which is

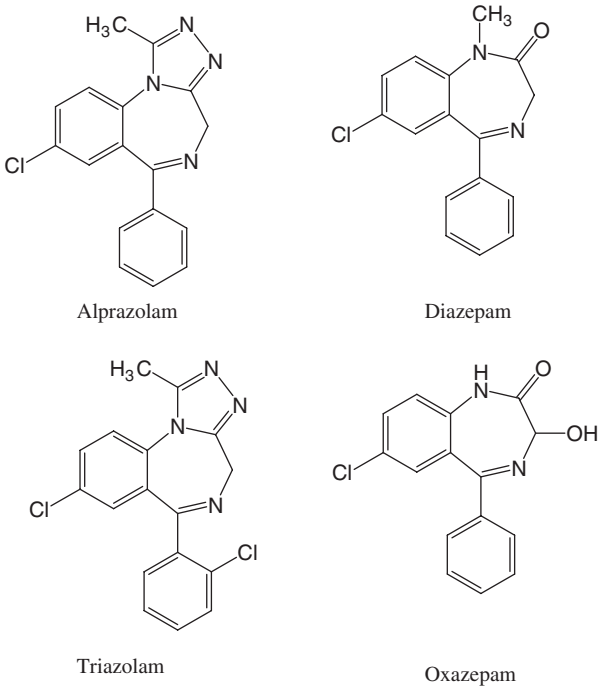


Fig. 2.3 Structures of common benzodiazepines

also a common metabolite of both diazepam and temazepam, is an active metabolite. Oxazepam is then conjugated and is excreted in urine as oxazepam glucuronide. Diazepam is also metabolized to nor-diazepam which is an active metabolite. Clorazepate is metabolized to active metabolite nor-diazepam which is then further metabolized to oxazepam. Chlordiazepoxide is metabolized to nor-chlordiazepoxide and demoxepam which are both active metabolites. Then demoxepam is further metabolized to nor-diazepam and then nor-diazepam is subsequently metabolized to oxazepam. Alprazolam is metabolized to two hydroxylated metabolites; 4-hydroxy-alprazolam and α-hydroxy-alprazolam. Both metabolites are active but the activities are lower than the parent drug. Therefore clinical activity of alprazolam is mostly due to the parent compound [17]. Major metabolites of commonly abused benzodiazepines are listed in Table 2.1.

4.2 Benzodiazepine Overdose and Fatality

Benzodiazepines are widely prescribed worldwide. Therefore, hospital admission due to benzodiazepine overdose is common. There is a positive association between benzodiazepine use and driver-responsible fatalities from motor vehicle accidents.

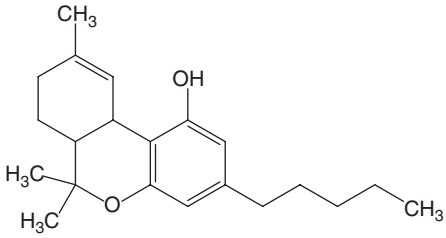
In England, benzodiazepine overdose caused 3.8% of all death caused by a single drug overdose [18]. Carlsten et al. reported that in Sweden, benzodiazepines were implicated in 216 out of 548 of the drug related suicides among the elderly (over 65 years) between 1992 and 1996. Death reports revealed that flunitrazepam and nitrazepam were implicated in 90% of the single benzodiazepine related suicides. The authors concluded that benzodiazepines, especially flunitrazepam and nitrazepam, are commonly encountered in suicide by the elderly and should be prescribed with caution in this age group of patients [19]. Martello et al. described the fatality of a 68-year-old woman due to ingestion of flurazepam. The postmortem heart blood flurazepam concentration was 2.8 μg/mL, while the urine concentration was 172 μg/mL in a 68-year-old woman [20].

5 Cannabinoids

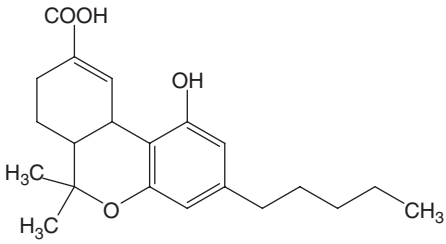
Psychoactive products obtained from the plant *Cannabis sativa* (marijuana) have been used for euphoric effect for over 4,000 years, and are currently the most widely used illicit drugs in the U.S. Cannabinoids refers to over 100 related compounds found in the extract of cannabis plant which are lipid soluble and the most psychoactive compound is Δ^9-tetrahydrocannabinol (THC). Marijuana cigarettes are made from the leaves and flowering tops of the plant, while hashish and hash oil are prepared from a concentrated resin and a lipid-soluble extract and THC is the most psychoactive component of marijuana. The most potent form of marijuana, known as sinsemilla, is prepared from dried parts of mostly indoor-grown female plants. When smoked, THC is quickly absorbed from the lungs into the bloodstream, from which it rapidly distributes into tissue. THC exerts its effect by binding to specific cannabinoid receptors in the brain. Interestingly, both THC and opioids produce an analgesic effect through G-protein coupled mechanisms that block propagation of neurotransmitters causing pain in the brain and spinal cord. It is assumed that the analgesic effect of THC may also be due to interaction of THC with delta and kappa opioid receptors [21].

5.1 Metabolism of THC

Pulmonary assimilation of inhaled THC produces maximum plasma concentrations within minutes and psychotropic effects reach a maximum after 15–30 min and may last for 2–3 h. THC is rapidly metabolized by cytochrome P 450 enzymes (mostly CYP3A4, CYP2C9 and CYP2C11) to 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH−THC), an equipotent psychoactive metabolite and also to 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC−COOH), an inactive metabolite. Smaller quantities of other metabolites have also been isolated. Usually THC−COOH is found in the urine in conjugated form. Chemical structures of THC and its major metabolite are given in Fig. 2.4.



THC



THC-COOH

Fig. 2.4 Chemical structure of THC (tetrahydrocannabinol) and its metabolite THC−COOH

5.2 THC Overdose

THC impairs cognition, psychomotor skill and driving performance in a dose related manner. Research has established that the presence of THC in blood, especially in higher amounts, are three to seven times more likely to be responsible for their crash as compared to drivers who had not used drugs or alcohol. Epidemiological studies established that combined use of THC and alcohol produces sever impairment of cognitive, psychomotor, and actual driving performance, sharply increasing the crash risk [22]. THC has been detected in the blood of drivers after fatal crashes. MacInnes et al. reported fatal coronary artery thrombosis associated with cannabis smoking [23].

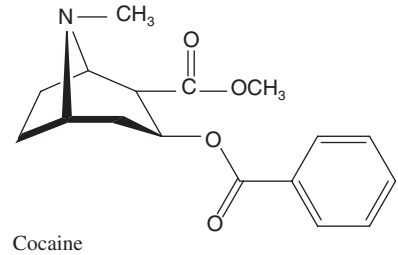
6 Cocaine

Cocaine is an alkaloid found in the leaves of *Erythroxylon coca*, a shrub indigenous to many parts of South America but primarily Bolivia and Peru. Indigent people of South America chewed coca leaf for recreational purpose for many centuries. Cocaine was first isolated from the coca leaf in 1855. Sigmund Freud famously proposed its use to treat depression and alcohol dependence, but the realities of cocaine addiction quickly brought this idea to an end. Currently, there is no prescription medication that contains cocaine. Cocaine is only used as a topical anesthetic in ear nose and throat surgery, in ophthalmologic procedure or in skin suturing.

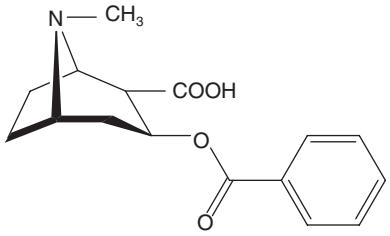
Cocaine exerts its pharmacological effects by blocking reuptake of the neurotransmitters dopamine and norepinephrine, which raises blood pressure, heart rate, and body temperature. Cocaine is a Schedule II drug due to its high abuse potential. Cocaine is abused as the hydrochloride salt which can be snorted. Crack cocaine is a form of cocaine which has not been neutralized by acid to produce the hydrochloride salt. Crack cocaine comes as rock crystal which can be heated and smoke can be inhaled for euphoria. The term "crack cocaine" comes from the cracking sound which crack cocaine produces during heating. Repeated abuse of cocaine may alter brain chemistry including dopamine, gamma-aminobutyric acid (GABA) and glutamate regulation of pyramidal cell activity [24].

6.1 Pharmacology of Cocaine

Cocaine has a short half-life (0.5–1.5 h) and is rapidly deactivated by plasma butyrylcholinesterase into ecgonine methyl ester. Another major metabolite of cocaine, benzoylecgonine, probably arise spontaneously in plasma by hydrolysis of cocaine in vivo. Benzoylecgonine along with ecgonine methyl ester represents major urinary excretion of cocaine. A small amount of unchanged cocaine can also be recovered in urine. A small amount is cocaine is also metabolized by liver enzymes into nor-cocaine. Other minor metabolites of cocaine include *p*-hydroxy-cocaine, *m*-hydroxy-cocaine, *p*-hydroxy-benzoylecgonine and *m*-hydroxy-benzoylecgonine [25]. Major metabolites of cocaine are listed in Table 2.1. Chemical structure of cocaine and its major metabolite benzoylecgonine are given in Fig. 2.5.



Cocaine



Cocaethylene

Fig. 2.5 Chemical structures of cocaine and benzoylecgonine

6.2 Abuse of Cocaine and Alcohol

Simultaneous abuse of cocaine and alcohol (ethanol) causes more toxicity compared to abuse of cocaine or alcohol alone and such combined use abuse results in significant increases in morbidity and mortality. The combined effect of cocaine and alcohol in humans is related to the formation of cocaethylene, which is formed by transesterification of benzoylecgonine by ethanol in the presence of liver carboxylesterase. Chemical structures of cocaine, benzoylecgonine and cocaethylene are given in Fig. 2.5.

6.3 Fatality from Cocaine and Cocaethylene

Cocaine is frequently encountered in fatal drug overdose. In a case report of a 26-year-old woman who died from recreational use of cocaine, the postmortem blood cocaine level was 330 μg/mL. This is an extremely high blood cocaine level. Blood levels of benzoylecgonine and ecgonine methyl esters were 50 and 18 μg/mL respectively [26]. Body stuffers, also referred to as "body packers" are drug smugglers, who swallow packets containing illegal drugs to escape detection by the authorities during border crossing or going thorough customs in an international airport. Sometimes these containers may break inside the body, causing a massive overdose which may often be fatal. This is referred to as "body stuffer's syndrome" and cocaine is the most commonly encountered drug. There are several fatal cases of cocaine overdose in body packers reported in the literature [27].

Mixing cocaine and alcohol is a deadly combination. Cocaethylene is found in plasma only after simultaneous abuse of cocaine and alcohol. Cocaethylene is psychoactive and has a plasma half-life three to five times longer than cocaine and, due to intense and prolonged euphoria, abusers prefer to mix cocaine with alcohol. However, cocaethylene may cause seizure, liver damage and affect the immune system. It also carries an 18- to 25-fold increase over cocaine alone in the risk of immediate death [28]. Cocaethylene is often found in high amounts in fatal overdoses of abusers.

7 Opiates

Opiates consist of naturally-occurring or semi-synthetic alkaloids derived from opium, which is found in the latex (a milky fluid) collected from immature seed capsules of poppy plants (*Papaver somniferum)* 1−3 weeks after flowering by incision of green seed pods. More than 20 alkaloids have been isolated from *Papaver somniferum* out of which three alkaloids − morphine, codeine and noscapine (antitussive) − are used in therapy. Morphine, the principal natural opiate, is the structural building block for many of the semi-synthetic opioids including heroin, oxycodone, oxymorphone, hydrocodone, hydromorphone, and levorphanol. Opioids

interact with the family of opioid receptors (mu, delta, and kappa). Opioid receptor agonists typically produce analgesia, while antagonists block this response. In addition to potent analgesic properties, opiates can also cause sedation, euphoria, and respiratory depression. which gives opiates a high abuse potential. Long-term use can lead to tolerance and both physical and psychological dependence.

Morphine is available for administration in oral form but its effect is usually diminished when given orally. Usually morphine is administered as an intravenous injection. However, codeine, hydromorphone and oxycodone can be administered orally. The major analgesic effect of codeine is due to its active metabolite morphine. Heroin has little oral bioavailability because it is subjected to complete first pass metabolism. The heroin abuser takes this drug by injection. Chemical structures of codeine and morphine are given in Fig. 2.6.

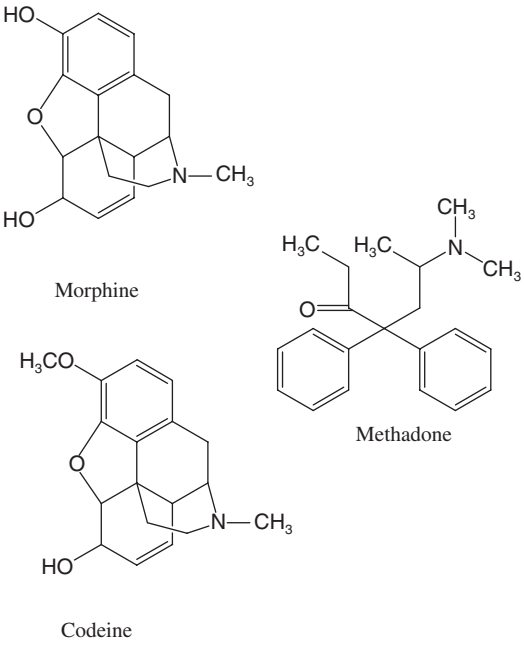


Fig. 2.6 Chemical structure of morphine, codeine, and methadone

7.1 Pharmacology of Opiates

Morphine is conjugated and excreted in the urine as morphine-3-glucuronide. Heroin is metabolized to 6-acetylmorphine and then to morphine by hydrolysis of ester linkage by pseudocholinesterase in serum and also in liver by human carboxylesterase-1 and carboxylesterase-2. A small part of morphine (less than 5%) is nor-morphine but the majority of morphine is excreted in urine as morphine-3-glucuronide. This metabolite is form by conjugation in the liver by the action of liver enzyme uridine diphosphate glucuronosyltransferase. Codeine is metabolized

to morphine in the liver mostly by CYP2D6 [29]. Hydromorphone is also excreted in urine mostly in the conjugated form but a small part of free hydromorphone can also be recovered in urine. Oxycodone is metabolized to oxymorphone which is then conjugated in the liver. Another metabolite of oxycodone is nor-oxycodone which is relatively inactive. Major metabolites of opiates are listed in Table 2.1.

8 Methadone

Methadone, a synthetic opioid, is structurally unrelated to the natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects as seen with natural opiates, including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin. Methadone is used clinically to relieve pain, to treat opioid abstinence syndrome, and to treat heroin addiction in the attempt to wean patients from illicit drug use. Methadone is available as a racemic mixture but most of activity is due to the R isomer. In addition, methadone also acts as agonist of *N*-methyl-D-aspartate receptors which may increase effectiveness of methadone in treating neuropathic pain. See Fig. 2.6 for chemical structure of methadone.

8.1 Pharmacology of Methadone

Oral bioavailability of methadone is 60–70%. Methadone is strongly bound to serum proteins, mostly α_1-acid glycoprotein. For treatment of heroin and opiate dependency, methadone can be administered orally once a day but for pain management more frequent dosing is needed. The elimination half-life of methadone is 15–55 h but the effect of analgesia lasts only for 4–6 h. Methadone is mostly metabolized in the liver by cytochrome P 450 enzymes, especially by CYP3A4 but also to a lesser extent by CYP2D6. Moreover, methadone is also metabolized in the intestines. The methadone half-life may be prolonged in approximately 10% of the Caucasian population who are poor metabolizers and who have low activity of CYP2D6 [30]. Patients taking methadone excrete both the parent drug and the major metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) in urine. Clinically, it is important to measure both compounds, as methadone excretion varies widely with dose, metabolism, and urine pH.

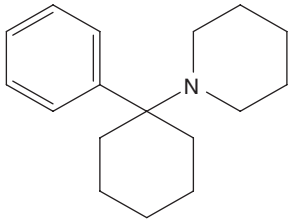
9 Phencyclidine

Phencyclidine (PCP) was developed in the 1950s as a human anesthetic but was discontinued soon thereafter due to serious psychological side effects. In contrast to amphetamine induced psychosis, PCP induced psychosis incorporates both positive

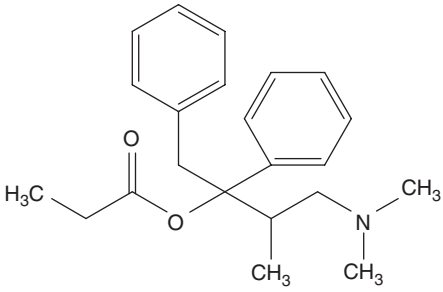
(hallucination, paranoia) and negative (emotional withdrawal, motor retardation) effects.

PCP undergoes extensive metabolism by liver cytochrome P 450 enzymes (especially CYP3A4) into several hydroxy metabolites including *cis*-1-(1-phenyl-4-hydroxycyclohexyl)piperidine, *trans*-1-(1-phenyl-4-hydroxycyclohexyl) piperidine, 1-(1-phenylcyclohexyl)-4-hydroxypiperidine and 5-(1-phenylcycloh exylamino)pentanoic acid. The elimination half-life of PCP varies significantly in humans (7–57 h; average 17 h) [31]. Chemical structure of PCP is given in Fig. 2.7.

Fig. 2.7 Chemical structures of PCP and propoxyphene



Phencyclidine (PCP)



Propoxyphene

10 Propoxyphene

Propoxyphene which is structurally similar to methadone and binds to opiate receptors is administered orally for treating mild to moderate pain and was approved by the FDA in 1957. Propoxyphene exists as an optical isomer where D-propoxyphene has analgesic activity and is used in pain management while the L isomer is devoid of analgesic activity and is used medically as an antitussive agent. Propoxyphene is used alone or in combination with acetaminophen for pain control. Propoxyphene has approximately 33–50% of the potency of codeine. After oral administration, peak plasma concentrations of propoxyphene can be observed after 2 h and the average plasma half-life is 15 h. Propoxyphene is metabolized by the liver enzyme mainly by CYP2D6 to nor-propoxyphene. Propoxyphene is both a substrate and an inhibitor of CYP2D6 and has pharmacokinetically important drug interactions

with drugs that are metabolized via CYP2D6. Nor-propoxyphene has a substantially longer half-life than propoxyphene and this metabolite tends to accumulate in plasma of patients with renal impairment. Nor-propoxyphene is an active metabolite and has more cardiac toxicity than propoxyphene and can initiate pulmonary edema, apnea, cardiac arrest and death. Propoxyphene should not be prescribed to patients who are suicidal or prone to addiction. Moreover, this drug should be prescribed with extreme caution to patients taking antidepressants or tranquilizers or who are abusing alcohol. Prolonged use of this drug may cause dependence. Unfortunately, due to the euphoric effect of propoxyphene, this drug is also abused [32]. See Fig. 2.7 for structure.

11 Methaqualone

Methaqualone is considered as a sedative hypnotic drug with pharmacological effects similar to barbiturates. This drug was originally synthesized as an antimalarial agent. Methaqualone was introduced in 1954 in the United States but due to its high abuse potential this drug was discontinued in 1984 and was classified as a Schedule I drug with no known medical use. In the 1960 s and 1970 s methaqualone was a popular street drug in the United States [33]. Methaqualone is known as Mandrax in South Africa. Although oral abuse of methaqualone is decreasing in Western countries, the practice of smoking methaqualone is a serious public health issue in South Africa, other parts of Africa and India [34].

12 Glutethimide

Glutethimide was introduced in the United States in 1954 as a safe alternative to barbiturates. However, this drug also has a high abuse potential and was widely abused in the United States. In 1991, glutethimide was transferred to a Schedule II drug which now has little medical use. Abuse of oral combination of glutethimide and codeine commonly referred to as “sets” was on the rise in the 1970s and 1980s in the United States. The glutethimide/codeine combination produces euphoric effect comparable to heroin but is longer in duration. This effect may be related to induction of liver enzyme, most likely CYP2D6, which is responsible for the metabolization of codeine to its more active metabolite morphine. Moreover, glutethimide may also inhibit conjugation of morphine to form the inactive metabolite morphine-3-glucuronide.

13 Conclusions

Amphetamines, cocaine, marijuana, opiates and to a lesser extent PCP are widely abused and are in the list for federal workplace drug testing. In addition, benzodiazepines and barbiturates are also abused. Methaqualone and gluthemide,

although widely abused in the past, are currently less abused. Knowledge of the pharmacology of these abused drugs is critical in understanding workplace drug testing.

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