Narcotic Analgesics and Common Drugs of Abuse

Clinical Correlations and Laboratory Assessment

Martin H. Bluth, MD, PhD[a,b], Matthew R. Pincus, MD, PhD[c,*]

KEYWORDS

• Drugs • Toxicology • Addiction • Pain • Clinical • Laboratory • Abuse • Analgesia

KEY POINTS

- Pain management is an evolving discipline; new formulations of narcotic analgesics mature to the marketplace with the promises of availing improved pain control, better dosing, and fewer side effects.
- These agents also avail an equal risk for abuse, which may mature as a result of physiologic tolerance, polypharmacy, metabolic factors, phramacogenomics, and economic concerns.
- Street chemists are adept at manipulating current and evolving drugs to more potent versions and creating new compositions of matter for consumption in the medical and illicit marketplaces.
- Clinical assessment is paramount to developing an index of suspicion of overdose, toxicity, or illicit drug use; the laboratory can support such investigations and guide therapy.
- As new agents pervade the health care system, the clinical toxicology laboratory keeps in step with adapting its technology and methodology to facilitate detection.

EXTENT OF USE OF DRUGS OF ABUSE

Over the last decade, there has been a general increase in the use of all drugs of abuse in the US population aged 12 years and over. The reported difference in illicit drug use from 2013 to 2014 has demonstrated an increase from 41.6 million users to 44.2 million, representing a greater than 6% increase, or 2.6 million new drug abusers, over 1 year alone. These agents include common illicit drugs including heroin, cocaine, and hallucinogens as well as nonmedical use of prescription drugs, sedatives, tranquilizers, pain relievers, and other agents.[1] The highest number of drug

[a] Department of Pathology, Wayne State University School of Medicine, 540 East Canfield, Detroit, MI 48201, USA; [b] Consolidated Laboratory Management Systems, 24555 Southfield Road, Southfield, MI 48075, USA; [c] Department of Pathology, SUNY Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA
* Corresponding author.
E-mail address: mrpincus2010@gmail.com

Clin Lab Med 36 (2016) 603–634
http://dx.doi.org/10.1016/j.cll.2016.07.013 **labmed.theclinics.com**

abusers occurs in the 15- to 39-year-age range, at almost 75%. Interestingly, individuals in the 40- to 59-year bracket comprise most of the remainder, comprising more than 20% of the overall number of drug abusers, a sizable fraction. Drug abuse does spare any age, race, gender, socioeconomic, employment, or educational status. In fact, illicit drug use in 13-year-old children increased by approximately 30% from 2013 to 2014 (275,000 to >350,000 nationwide), and persons aged 26 and older have a 20% to 25% lifetime probability of using cocaine no matter whether they be full time, part time, or unemployed.[1] Because all persons are at risk for drug abuse, including prescribed, nonprescribed, and illicit substances, understanding the general and specific biological and physiologic effects of such pharmacopeia, in addition to absorption, distribution, metabolism, and excretion can help health care providers to select appropriate medications, either alone or in concert with other agents, as well as use appropriate ancillary clinical toxicology laboratory testing approaches to manage their patient populations.

APPLICATION OF THE CLINICAL TOXICOLOGY LABORATORY

The role of the clinical toxicology laboratory provides substantial support to patient pain management. It can facilitate objective information on whether the patient is (1) taking what the physician prescribed and (2) if he or she is taking something else. However, the laboratory results are not to be considered the be all and end all of whether a patient is adhering to clinical instruction or compliant with medication prescribing habits. As with most drugs, it is important to understand that the results of routine urine drug testing are not intended for use to diagnose, manage, treat, cure, or prevent any disease as a sole independent ancillary support application in lieu of the patient–physician relationship nor for application to forensic, employment, or court proceedings unless orchestrated through appropriate channels (www.samhsa.gov). Appropriate clinical management resides solely with the patient's primary care provider. However, laboratory results are intended and appropriately situated to provide laboratory supplemental data for discretionary use, in conjunction with other clinical patient profiles, presentations, signs, symptoms, history, and physical findings obtained by the patient's primary care provider. Furthermore, to this end, parent drug or metabolite concentrations are subject to many metabolic factors, including but not limited to hydration, kidney and liver function, time and dose of drug ingestion, and pharmacogenomics. For example, it is plausible that a patient who was prescribed codeine for pain management resulted in a urine test negative for codeine but positive for hydromorphone. It could be that this patient, who is a "rapid metabolizer" ingested codeine as prescribed, and catabolized codeine to morphine by *O*-demethylation, which also exerts its effects on its congeners—dihydrocodeine, ethylmorphine, hydrocodone, or oxycodone—but carried the polymorphically variant CYP2D6 allele or multiple alleles thereof, thereby fostering rapid conversion to hydromorphone, which is what was resulted in the patient's urine test.[2] In such an instance, varying the time of last ingestion to collection, in addition to being mindful of the other factors listed above, could shed light on identifying personalized testing that should be considered in performing urine drug testing. Understanding the results of such tests, which can differ from one patient from another, are necessary even when both are prescribed the same drug regimen. To this end, studies by Smith and colleagues[3] demonstrated that volunteers who ingested opiates and were assessed for urine parent drug and their metabolites (hydrocodone, hydromorphone, oxycodone, and oxymorphone) differed considerably from one another based on dose, time of collection, and analysis method used.

Regarding the methodology used in the clinical toxicology laboratory, there are different approaches that can be used to obtain pain medication analyte measurements in body fluids (blood, urine, saliva) including chromatographic (thin layer chromatography [TLC]; high-performance liquid chromatography), enzyme immune assay–based (enzyme-mediated immunologic technique; florescence polarization immunoassay), and gas or liquid chromatography based mass spectrometry (GS/MS or LC/MS, respectively). In general, basic enzyme and chromatographic tests are used for drug screening and are sometimes found in the point of care or clinical office setting. However, screening technologies are not very specific. Therefore, when screens are positive they are subsequently confirmed for the presence of specific drugs via GC/MS or LC/MS because these technologies use high complexity methodologies that assess the mass to charge ratio of each analyte, which can serve a "molecular fingerprint" for various entities including specific drugs of abuse (see Yan Victoria Zhang and colleagues article, "Liquid Chromatography–Tandem Mass Spectrometry: An Emerging Technology in the Toxicology Laboratory," in this issue).

GENERAL ASPECTS OF THE MECHANISMS OF ACTION

The major drugs of abuse include those prescribed in analgesia.[4] They can be generally divided into the natural and semisynthetic opioids (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, heroine, buprenorphine, norbuprinorphine, meperidine), synthetic opioids (fentanyl, norfentanyl, methadone and EDDP [2-ethylidene-1,5,dimethyl-3-3-diphenylpyrrolidine; a methadone metabolite], tapentadol, tramadol, and other new composition of matter).[5,6] These drugs, with the exception of the barbiturates and the cannabinoids, are all basic amino group–containing compounds, most of which also contain benzene rings. The steric relationship of the amino group with respect to the aromatic benzene rings is rather similar, especially in cocaine, the opiates, and methadone. As might be expected, these compounds can cross-react, although with lower affinities, with each other's target receptors, and as such may also cross-react in toxicology screens that use immunoassay detection methodologies, yet are resolvable through mass spectrometry confirmatory testing approaches.[7]

The primary physiologic mechanisms of action of these drugs are not completely understood, but some rudimentary knowledge has been gained as to some of the main targets of these drugs. Many of these drugs act directly on dopaminergic and norepinephrinergic neurotransmitter systems, especially the limbic system, which is associated with general pleasure seeking and can precipitate behavior to that end.[8]

Fig. 1 depicts the likely mechanism of action of several of the most important drugs in the system. The class of amphetamines, closely related structurally to dopamine and the catecholamines, and cocaine seem to cause release of dopamine from the vesicles at the axonal side of the synapse, which may partially be responsible for the production of a pleasant sensation (so-called "high") in many individuals.[9] The tricyclic antidepressants stimulate pathways that use norepinephrine as the neurotransmitter. These pathways, like the dopaminergic pathways, are involved in arousal and pleasure seeking. In this case, the tricyclic antidepressants, rather than promoting release of the neurotransmitters, block the reuptake of norepinephrine into the vesicles on the axonal side of the synapse. They also may exert nonspecific reuptake blockade of dopamine in the dopaminergic pathways.[10] It is of great interest that, paradoxically, the tricyclic antidepressants such as imipramine (Tofranil) have been used successfully to treat the effects of cocaine, although success with benzodiazepine tranquilizers (oxazepam) in conjunction with cortisol synthesis inhibitors

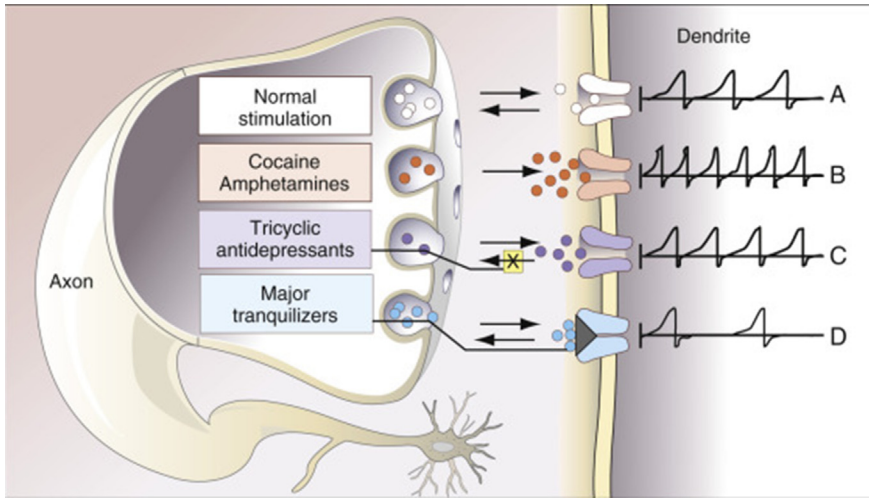

Fig. 1. Possible mechanisms of action of drugs of abuse and some therapeutic drugs on sympathomimetic amine (dopamine and norepinephrine) pathways. (A) Normal neural transmission. A nerve impulse is conducted down the axon to the terminal boutons at the nerve ending. Vesicles, represented by the round gray structure, release their contents of neurotransmitter, here dopamine, represented by small white circles. Dopamine molecules traverse the synaptic cleft and bind to dendritic receptors, initiating action potentials (*at right under "dendrite"*) in the dendrites. Notice the *arrows* showing that dopamine is both released and taken up by the vesicles. (B) In the presence of cocaine and amphetamines, enhanced release of neurotransmitter (*red circles*) from vesicles occurs, increasing the rate of firing in the dendrites. (C) Tricyclic antidepressants block (*arrow with "X" in yellow box*) reuptake of the neurotransmitter (*purple circles*), in this case norepinephrine and, less specifically, dopamine, causing more neurotransmitter to "recycle" to the dendritic receptors, resulting in increased firing. (D) Some of the neuroleptics act by blocking (*gray wedge*) postsynaptic dendritic receptors for dopamine (*blue circles*), causing decreased firing. (*From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 333.e2; with permission.)

(metyrapone) have been described.[11] Further use of benzodiazepines have been posited to enhance γ-aminobutyric acid (GABA) responses either via increasing receptor expression density or channel gating efficiency.[12] To this end, major tranquilizers such as haloperidol (Haldol) and chlorpromazine, used to treat psychotic states such as schizophrenia, seem to block attachment of dopamine to the dendritic receptors in the synapse, thereby blocking the stimulatory effects of dopamine. Associated with many dopaminergic neurons are inhibitory neurons that use GABA as their neurotransmitter. It seems that many benzodiazepine receptors exist on these neurons, causing potentiation of GABA at the synapses in this system, reducing the dopaminergic effects of the stimulatory pathways on the limbic system. Thus, some of the tranquilizing effects of diazepam (Valium) and other benzodiazepines can be explained.

Widely distributed throughout the central nervous system (CNS) and periphery are a variety of opioid receptors classified mainly as μ-, δ-, κ-, and ϵ-receptors.[13] The μ-receptors seem to be rather specific for morphine and heroin, both of which produce a general analgesic state. Many of the drugs of abuse also act on 2 other major

pathways in the brain: those using serotonin (serotonergic) and those using *N*-methyl-D-aspartate (NMDA) as their neurotransmitter. Neurotranmission by serotonin occurs by its binding to the 5-hydroxytryptamine (5-HT) receptor on the dendritic side of the synapse. There is a rather wide range of 5-HT receptors, not all of which produce the same physiologic effects. The major ones seem to be the 5-HT_1 and 5-HT_2 receptors. The serotonin pathways encompass a rather wide swath of the brain and even the spinal cord. This neurotransmitter is the principal one for the limbic system and, in addition, the basal ganglia, especially the amygdala that is involved in aggressive behavior. As mentioned, the limbic system is involved in pleasure seeking and pleasure reinforcement. Serotonergic pathways also extend to the hippocampus and are involved in memory. As a neurotransmitter in the spinal cord, serotonin induces muscle contraction. NMDA pathways are more involved in nociceptive (pain) pathways and are involved in memory and neuronal plasticity.[14] They have been found to be involved in chronic pain reinforcement. Blockade of NMDA pathways by drugs of abuse can therefore remove this perceived undesirable effect.

DRUG METABOLISM

Many drugs are converted to metabolites, some of which are pharmacologically active and some inactive. Much of this conversion occurs in the extramitochondrial, microsomal system present in hepatocytes. This metabolic system is mainly an oxidative one that uses a series of oxidative enzymes that, in turn, use a special cytochrome system: cytochrome P450.[15] This extremely critical cytochrome system, and genetic polymorphism of the cytochrome P450 enzymes, affects an individuals particular response to a drug, including toxicity and an adverse drug reaction. It is now possible to test individuals for their ability to metabolize specific drugs by amplification of their genes encoding cytochrome P450. Certain amino acid substitutions in this protein cause it to be very active in drug metabolism (ie, rapid inactivation of the drug). This implies that the patient may need substantially higher doses to achieve a therapeutic level, or that it may be necessary to use another less rapidly metabolized drug (see Daniel A. Schwarz, M.P. George, Martin H. Bluth's article, "Precision Medicine in Toxicology," in this issue).

Because the excretion of many drugs depends on the integrity of the liver and the cytochrome P450 system, in patients with liver failure owing to passive congestion, hepatitis, cirrhosis, and the like, the effective half-life of the drug is increased, making it necessary to lower the divided dose of the drug. Conversely, some drugs induce the intracellular synthesis of the microsomal enzymes, leading to diminished half-life values, so that it may be necessary to increase the divided dose. In certain cases drugs can induce microsomal enzymes to facilitate its own metabolism (ie, phenobarbital, phenytoin) so that its concentration levels do not obey first-order kinetics, as well as others that are differentially catabolized through phase I and/or phase II metabolic pathways.[16] In instances in which the levels of a drug metabolized in the liver are higher than the highest therapeutic value, reductions in the levels may be induced by administering low levels of such a drug to induce the microsomal system. Furthermore, although many narcotic analgesics are principally metabolized by the liver, there are those (ie, gabapentin, pregabalin) that are metabolized by nonhepatic organ pathways.[17]

These summaries of some of the general principles of drug administration should be helpful in the interpretation of values clinically and should permit a better understanding of the subsequent discussion of specific analgesic drugs, most frequently prescribed for pain management, yet are also subject to abuse potential.

COCAINE

Cocaine is derived from the coca plant and has enjoyed much popularity as an additive to certain foods. At the beginning of the 20th century, it was used in Coca-Cola, but owing to its addictive effects, this practice was discontinued. Cocaine is a derivative of the alkaloid ecgonine (ie, the methyl ester of benzoylecgonine) and can metabolize to benzoylecgonine, as shown in **Fig. 2**. The normal route of administration of cocaine is nasal (ie, inhalation, snorting), such that the drug passes through the nasal membranes. A particularly potent form of cocaine, called "crack," is the free-base form that passes rapidly across the nasal membranes such that, for a given dose, most or all of it enters the bloodstream rapidly. The half-life of cocaine is 1 to 2 hours, and the parent compound and its metabolites are usually cleared from the body within 2 days.

It is estimated that as many as 25 million people in the United States have used cocaine at least once[18]; fortunately, most of these individuals do not continue. Fatalities from cocaine abuse are of 2 types: direct toxicity of the drug and crime related to the illicit acquisition of the drug. Up to 25% of myocardial infarctions in patients between the ages of 18 and 45 have been attributed to cocaine abuse.[18]

Cocaine has been used medically to induce local anesthesia during nasopharyngeal surgery. However, in large doses, it induces a euphoric state (the "high" experienced by the user) and may also induce hallucinatory states. It can also promote violent behavior.[19] Many of these results can be explained by cocaine's dopaminergic effects. One study[20] suggests that cocaine induces increased calcium ion influx in dopaminergic neurons. The increased intracellular calcium activates phospholipases that possibly act as second messengers in causing ultimate release of dopamine in synapses. Prolonged action of phospholipases, however, ultimately causes cell death. In the previously mentioned study, in fact, cocaine was found to be neurotoxic. It also has a general cytotoxic effect from formation of an *N*-oxide free radical produced in the metabolism of this compound in the liver. It seems then that, over time, cocaine induces neuronal loss. In addition, binding of cocaine to cell receptors in the limbic system induces synthesis of cyclic adenosine monophosphate that seems to be critical in activating cell processes involved in dopamine release.[21] Cocaine may also block the reuptake of dopamine at the axonal side of the synapse, similar to tricyclic antidepressants (see **Fig. 1**). As if becoming toxic from cocaine abuse was not sufficient, many cocaine abusers consume this drug together with alcohol. Ethanol becomes esterified to cocaine in the liver to form cocaethylene, which blocks reuptake of dopamine in dopaminergic pathways more effectively than does cocaine and causes pronounced

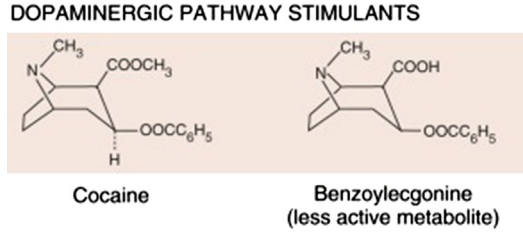

Fig. 2. Chemical structures of dopaminergic pathway stimulants. (*From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 332.e2; with permission.)

vasoconstriction of the coronary arteries, inducing increased myocardial oxygen demand. This cocaine derivative is deadlier than either cocaine or ethanol alone.

Other studies[18] further indicate that prolonged use of cocaine results in cardiotoxicity—that is, cocaine can cause progressive atherosclerosis and causes constriction of the coronary arteries that can, in turn, induce myocardial ischemia and sometimes frank infarction. Cocaine has been found to induce sympathomimetic effects on the myocardium by increasing heart rate. At the same time, it induces increased vasoconstriction. The net effect is increased chronotropy and afterload, resulting in increased oxygen demand by the myocardium. At the same time, cocaine induces platelet aggregation and stimulates production of plasminogen activator inhibitor. These events all predispose to development of myocardial infarction.

One highly disturbing aspect of cocaine abuse is that cocaine passes readily across the placenta and also into the lactating mammary gland and is readily passed from mothers to nursing infants. Often in the hospital setting, mothers receive the drug from dealers and breastfeed their newborn babies, who are therefore maintained on this drug. Cocaine causes mental retardation, delayed development, and strong drug dependence in newborns. It can also produce malformations in utero. According to the 2012 Survey on Drug Use and Health, 5.9% of pregnant women use illicit drugs, resulting in more than 380,000 offspring exposed to illicit substances.[22]

Cocaine has not been considered classically to be an addictive drug, because it does not cause the true physical dependence typical of abusers of barbiturates and opiates. However, the high produced by the drug is extraordinarily reinforcing, so that the drug-seeking behavior of the cocaine and opiate abuser is similar. Evidence in experimental animals suggests that cocaine can induce the release of β-endorphins that bind to μ-receptors in the limbic system. This induces a pleasant and positive feeling of reinforcement. Clinically, patients who are overdosed with cocaine may become violent and irrational, requiring sedation. One such treatment for patients in hyperexcitable states with cardiac symptoms such as palpitations is one of the benzodiazepines. Thus, it is not uncommon to find cocaine and a benzodiazepine (ie, oxazepam) in the urine of cocaine addicts.[11] Occasionally, overdosed patients will become obtunded or comatose. The treatment for these patients is usually supportive. Additionally, antidepressants, including the tri/tetracyclics, selective serotonin reuptake inhibitors, and the cortisol synthesis inhibitor metyrapone have been found in certain studies to inhibit some of the undesirable effects of cocaine and have been used in the treatment of cocaine abuse.

The half-life of cocaine, as stated, is approximately 1 to 2 hours. It is metabolized to more polar compounds that have significantly less potency than the parent compound. These metabolites have longer half-lives and, with techniques such as GC/MS, can be detected up to 48 hours after administration of the drug. The immunoassay methods can detect the drug for about 24 to 36 hours after administration. Certain metabolites (benzoylecgonine cocaine derivative) can be detected in urine for 3 to 5 days after administration. If a patient has inhaled cocaine free-base (“crack”), it is possible to detect the parent compound, cocaine, by TLC up to several hours after administration, owing to the high doses of drug present.

THE OPIATES

The primary medicinal use of opiates such as codeine and morphine is to diminish or eliminate pain in a patient. As noted, there are several classes of opiate receptors that are involved in the modulation of pain. These receptors are classified as μ, κ, δ, and ϵ. The endogenous ligands for each of these receptors are the antinociceptive

peptides: endomorphin (Tyr-Pro-Trp-Phe-NH_2) for μ receptors, dynorphins A (Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys) and B (Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr) for κ receptors, Met- and Leu-enkephalin (Tyr-Gly-Gly-Phe-Met and Tyr-Gly-Gly-Phe-Leu) for ϵ receptors and deltorphin (Tyr-D-Met-Phe-His-Leu-Met-Asp-NH_2) and Met and Leu-enkephalin for δ receptors. Note that the first 5 amino acids of dynorphin are identical to those of Leu-enkephalin, suggesting a possible reason for the binding of enkephalin to κ receptors. The exogenous opiates, that is, morphine, codeine, fentanyl, and others, whose structures are shown in **Fig. 3**, are known to be agonists, primarily, for μ receptors. As can be seen in this figure, morphine, codeine, heroin, oxycodone, and buprenorphine have similar structures. In fact, morphine is a metabolite of heroin, the diacetyl precursor of morphine.

A major target for each of the endogenous opiate peptides and for the exogenous agents is the main pain pathway, that is, the spinothalamic tract. This neural pathway carries nerve impulses from peripheral pain receptors to the peripheral nerves that innervate them to the posterior horn of the spinal cord where the nerves synapse to ascending fibers in the spinothalamic pathway. These nerves travel to the next spinal level where they cross the midline and then travel to the medulla as the lateral lemniscus that synapses in the thalamus (mainly in the ventroposterior nucleus) and then projects to the cortex where pain perception takes place. Activation of the opioid

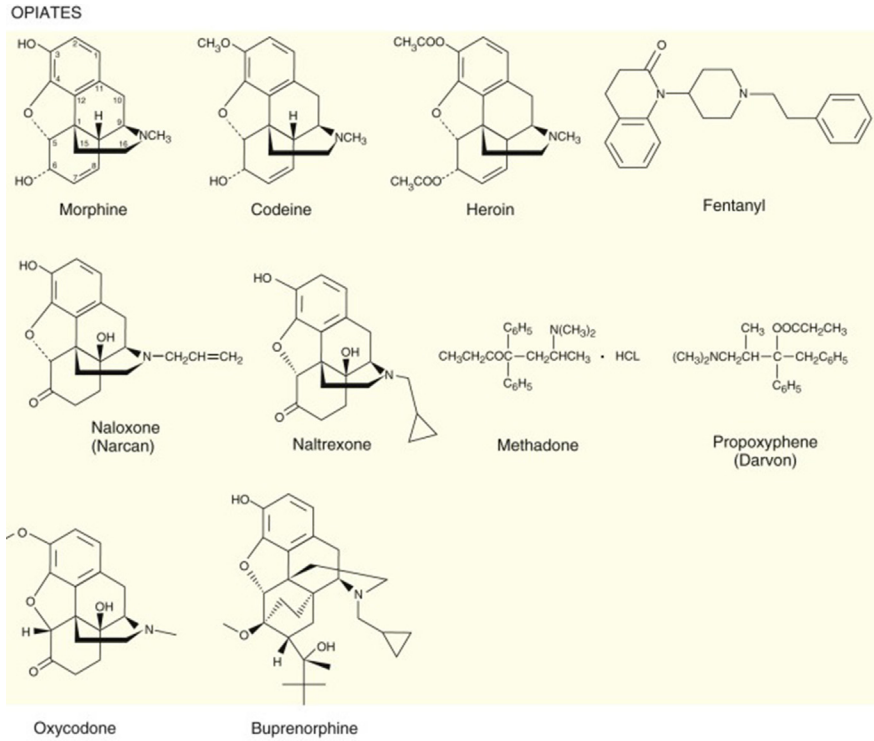

Fig. 3. Chemical structures of opiates. (*From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 331.e2; with permission.)

receptors that occur at these synapses results in hyperpolarization of the dendritic side of the synapses, blocking nerve conduction, thereby diminishing the sensation of pain.

In addition, it seems that the opioid receptors also play another major role in pain modulation via the activation of descending tracts that emanate from the midbrain in the periaqueductal gray area and travel to nuclei in the median raphe of the medulla. After synapsing with these nuclei, these tracts synapse at interneurons in the posterior horn of the spinal cord where they activate the release of GABA, resulting in inhibition of nerve conduction in the spinothalamic tract. Normally, these pathways are quiescent, but release of any of the endogenous antinociceptive peptides or introduction of exogenous drugs such as morphine or codeine, results in removal of inhibition of these pathways, again resulting in inhibition of nerve conduction in the spinothalamic pathway with diminished perception of pain.

Morphine and Heroin

Morphine, a μ receptor agonist, in addition to acting on pain pathways as described, further acts by binding to μ-receptors in the limbic system (CNS), mainly in the nucleus accumbens and the ventral tegmental area, resulting in an analgesic state. Binding of morphine and the other opiates to the μ-receptor inhibits the release of GABA from the nerve terminal, reducing the inhibitory effect of GABA on dopaminergic neurons. The resulting increased activation of dopaminergic neurons results in sustained activation of the postsynaptic membrane, causing a sense of euphoria. On the molecular level, binding of morphine to these receptors activates a cell signaling cascade via G-protein activation that results in elevated expression of many transcriptionally active proteins such as ERK, jun, and fos, and superactivation of adenyl cyclase resulting in high intracellular levels of cyclic adenosine monophosphate.[23] Besides being used as a major analgesic, morphine (ie, Dilaudid) is important in treating acute congestive heart failure by lowering venous return to the heart (ie, it is a powerful preload reducer by causing increased splanchnic pooling of blood).

Heroin induces a pleasant, euphoric state and is highly addictive both physically and psychologically. As can be seen in **Fig. 3**, heroin is a diacetyl form of morphine. This characteristic facilitates heroin's crossing the blood–brain barrier, allowing it to reach higher concentrations in the CNS. Withdrawal from this drug is exceedingly difficult, with a myriad of symptoms such as hypothermia, palpitations, cold sweats, and nightmares. This is a true physical dependence, the molecular basis for which is not fully understood. It seems that the dependence is strongly linked to the number of cell surface μ-receptors.[23]

This class of compounds exhibits certain important paradoxic effects on the parasympathetic nervous system. These drugs exert a procholinergic effect on the eyes and on blood vessels in the periphery (ie, they cause constriction of pupils ["pinpoint pupils"] and peripheral vasodilation). In contrast, in the gut they lower gastrointestinal (GI) motility (ie, they exhibit anticholinergic effects in the GI tract). This fact enables rapid diagnosis of heroin or, in general, opiate abuse in a patient brought to the emergency room in an obtunded or comatose state. These patients typically have severe miosis (pupillary constriction). Although the sign is not useful in acute diagnosis, constipation commonly occurs.

Administration of heroin occurs via the intravenous route. Addicts are readily recognized by the presence of needle tracks on their arms and hands and by extensive thrombosis of their peripheral veins. The half-life of heroin via the intravenous route is about 3 minutes, and the effects of the drug last approximately 3 hours. Heroin is almost immediately hydrolyzed by cholinesterase and arylesterase to

6-monoacetylmorphine (6-MAM), which occurs in plasma, erythrocytes, and liver. 6-MAM, is reported to have a half-life of 10 to 40 minutes and can be detected in urine up to 24 hours after intake. Heroine, via 6-MAM, is further metabolized to morphine, which has a half-life of 2 to 4 hours and can has a detection window in urine for approximately 2 to 4 days after ingestion. Morphine can be further conjugated to yield morphine-3-glucoronide (M3G), which can be detected in urine for up to 5 days, and other glucoronidated forms (ie, morphine-6-glucuronide). In general, 60% to 80% of heroin is excreted as morphine or M3G.[24] Thus, urine toxicology testing for heroin and its metabolites (6-MAM, morphine) are often performed in concert to determine the plausibility of heroin administration in the context of urine drug testing, which results as positive for morphine and its metabolites (**Fig. 4**). This approach has also been beneficial for those ingesting poppy seeds, which also convert to morphine, to clarify confusion of suspected heroin ingestion in this regard.[25,26]

Overdoses of heroin are extremely dangerous and can cause severe obtundation, coma, respiratory arrest, hypotension (secondary to histamine release), and cardiac arrhythmias. One of the most common acute therapeutic modalities for heroin overdose is intravenous treatment with naloxone (Narcan; see **Fig. 3**), a strong competitive antagonist to the action of heroin. Naloxone can be detected in urine approximately 2 days after ingestion.

Methadone

Heroin addiction, as a chronic problem, is treated pharmacologically with a partial agonist of heroin—methadone. This interesting compound, whose structure is shown in **Fig. 3**, binds competitively with morphine to μ-receptors in the brain. However, although it can become addictive, the addictive effects are less than those of

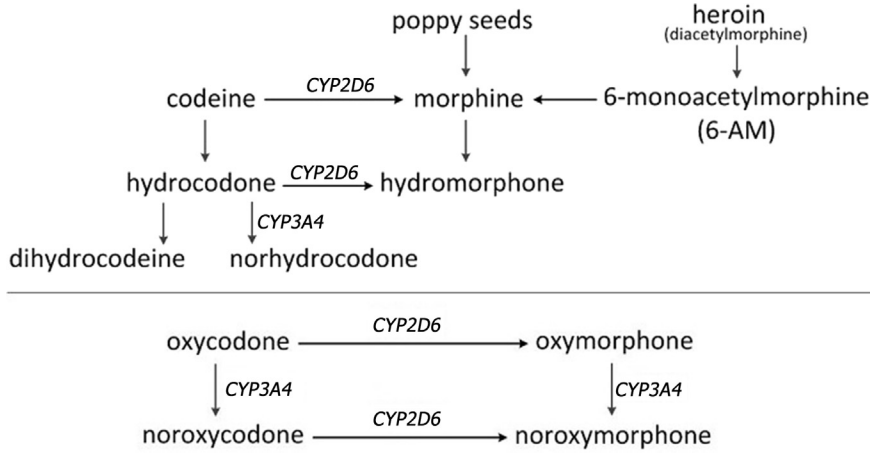

Fig. 4. Opiates and opioid metabolism. Shown in *italic* are the major cytochrome P450 enzymes involved in phase I metabolism; patterns of drug metabolites may reflect the metabolic phenotype of the patient. Actual proportions of individual metabolites will vary. Phase II reactions (eg, glucuronide conjugation) are not shown but are prominent for most compounds. (*From* ARUP Consult https://arupconsult.com/https://arupconsult.com, an ARUP Laboratories test selection tool for healthcare professionals.)

equivalent concentrations of heroin, possibly because its binding affinity is lower, so that it induces less of an effect than heroin. Thus, administration of methadone to heroin addicts allows them to experience the effects of heroin but in a modulated manner. By gradually lowering the methadone dose, physical dependence becomes reduced, and it seems that a trough serum methadone level greater than 100 ng/mL is adequate for effective methadone maintenance.[27]

However, it should be noted that addiction to methadone can also occur. In toxicology laboratories, the most common request received for methadone screens comes from methadone clinics to test whether a patient is administering methadone or has relapsed into taking heroin. Methadone can be distinguished from the opiates by many detection methods—TLC, enzyme-mediated immunologic technique, and florescence polarization immunoassay detects each drug with high specificity. Confirmation via GC/MS and LC/MS is also used and can detect methadone in urine approximately 3 to 5 days after ingestion. Methadone is further metabolized to EDDP. Recent studies have reported the usefulness of methadone-to-EDDP ratios to monitor for patient compliance.[28]

Another opiate antagonist is naltrexone, whose structure is shown **Fig. 3**. The primary effect of this drug is to lower the euphoria experienced by opiate abusers. However, it has no effect on opiate craving by drug abusers. In contrast, it has been found to be effective in reducing the physical dependence of patients treated with the drug; however, to achieve abstinence, psychosocial support of the patient is required. Surprisingly, naltrexone has been found to be effective in the treatment of alcohol dependence; in particular, it has been found to reduce relapse rates after abstinence and to reduce heavy drinking to lower levels of consumption. The half-life of naltrexone is about 4 hours. Treatment of opiate abuse generally requires daily administration (ie, 50 mg/day) and excretion is via urine with a detection window, similar to naloxone, of 2 days post ingestion.

Codeine and Analogs

The structure of codeine is similar to that of morphine and heroin (see **Fig. 3**). Codeine acts in a manner similar to that of morphine and is used as a milder analgesic and as an antitussive. Codeine metabolism is complex and can yield metabolites that are prescribed drugs themselves, which can be synergistically administered for maximal pain relief. As shown in **Fig. 4**, codeine can metabolize to morphine or hydrocodone. Hydrocodone in turn can be metabolized to hydromorphone as well as dihydrocodiene and norhydrocodone. Of interest is that morphine can also further metabolize to hydromorphone. Thus, it is not uncommon for a clinician to prescribe codeine to a patient whose urine drug test results as negative for codeine but positive for hydromorphone. This result can easily introduce suspicion of diversion of codeine and/or surreptitious ingestion of morphine. Therefore, appropriate understanding of opiate pathway metabolism can mitigate such concerns.

Dextromethorphan

Dextromethorphan (D-3-methoxy-*N*-methylmorphine), an analog of codeine, is the active component of cough syrups because of its antitussive effects. Recently, there has been a "run" on cough medicines by addicts, who can obtain them legally and then consume quantities sufficient to reach their desired euphoric state. Unlike codeine, dextromethorphan is believed generally not to be addictive, although cases of drug dependency have been documented. For therapeutic use, the recommended dose of dextromethorphan is 15 to 30 mg given 3 to 4 times per day. Moderate intoxication is achieved at about 100 to 200 mg, and heavy intoxication is reached at

around 1500 mg.[29] It is surprising to note that dextromethorphan does not have analgesic properties because of its lack of affinity for μ-, κ-, and δ-receptors. It has been found to induce the release and to block the reuptake of serotonin. Similar to the action of phencyclidine (PCP), discussed elsewhere in this article, dextromethorphan has also been found to block NMDA receptors that are critical for neuronal plasticity and memory and are involved in central pain pathways in the brain.[14] Dextromethorphan is readily absorbed from the GI tract and, in about 85% of individuals, is rapidly metabolized to dextrophan, an active metabolite, and D-hydroxymorphinane via the 2D6 cytochrome P450 isozyme. It is dextrophan that has a high affinity for NMDA receptors, so that most individuals experience PCP-like effects (ie, euphoria; tactile, auditory, and visual hallucinations; paranoia, altered time perception; and general disorientation). For the 15% of individuals who are slow metabolizers of dextromethorphan, these effects are much less pronounced and are replaced by sedation and dysphoria.[29] Overdoses of dextromethorphan can result in mainly neurologic effects, such as lethargy, or, conversely, hyperexcitability, ataxia, slurred speech, tremors and fasciculations, hypertonia and hyperreflexia, and nystagmus, as well as either pupillodilation or pupilloconstriction. Diaphoresis may also occur. In addition, cardiovascular sequelae include tachycardia and hypertension. Unfortunately, a number of antitussives contain, in addition to dextromethorphan, anticholinergic agents such as chlorpheniramine. Thus, abuse of antitussive medication can give rise to such symptoms as tachycardia, mydriasis, flushed skin, urinary retention, and constipation. Megadoses of dextromethorphan can occasionally produce a false-positive screening test for PCP or opiates, which can be confirmed with GC/MS or LC/MS.[30] Dextromethorphan can be detected in urine after ingestion with a detection window of 1 to 2 days.

Oxycodone

This drug is effective in reducing pain, especially pain associated with malignancy. Its structure is shown in **Fig. 3**, where it can be seen to be similar in structure to codeine with the difference that there is a keto rather than a hydroxyl group at the 7-position (lower cyclohexone ring) and a hydroxyl group rather than a hydrogen atom at the carbon between the 2 bridgehead carbons. On an empty stomach, pain diminution commences within about 15 minutes after oral drug administration. Peak serum levels are achieved in about 1 hour. The slow release form of oxycodone is oxycontin that achieves peak serum levels in about 3 hours. Although there is some controversy about the site of action of oxycodone, that is, primary action on κ, rather than μ, receptors, oxycodone does bind to μ receptors and one of its metabolites, oxymorphone, is known to have a high affinity for μ receptors.[31] The half-life for oxycodone is about 3.2 hours and for oxycontin is 4.5 hours. Metabolites of oxycodone are α- and β-oxycodol, oxymorphone, α- and β-oxymorphol, noroxymorphone, noroxycodone, α- and β- noroxycodol, and noroxymorphone (*N*-desmethyloxycodone). Most of the parent compound, as with other opioids, and its metabolites are excreted in the urine with a detection window of 2 to 4 days after ingestion.

As with morphine and codeine, oxycodone, especially at high doses, can induce euphoria and a sense of well-being, and, like the other opiates, it induces a true physical dependence. At high doses, side effects are particularly pronounced, and these include fatigue, dizziness, constipation, vomiting, anxiety, shallow breathing and apnea, hypotension, meiosis, circulatory collapse, and death. Withdrawal from oxycodone includes such symptoms as myositis, anxiety, nausea, insomnia, fever, hypogonadism, and hormonal imbalance. Given the side effects and the physical consequences of withdrawal, it is difficult to fathom the appeal of abuse of this drug.

Nonetheless, abuse of oxycodone has grown to the point where it has now been added to the roster of drugs of abuse that are routinely assayed for mainly in urine.

Buprenorphine

Although, like oxycodone, this prescription drug has become a drug of abuse, buprenorphine exerts a mixed agonist–antagonist effect on opiate receptors. It has some opiate activity on μ receptors, but it is purely an antagonist on κ and δ receptors. Its major use is the same as for methadone in treating addiction to opiates, but is also used in the treatment of pain. Because it has partial agonist activity, it does not cause life-threatening respiratory depression as is true of the agonists like morphine. It undergoes extensive metabolism in the liver and, therefore, excretion is via the hepatobiliary system in contrast with oxycodone, whose excretion is almost completely via the urinary tract. Thus, renal failure does not result in accumulation of buprenorphine in serum, although it does cause increased levels of oxycodone. Treatment of patients with buprenorphine for addiction is carried out in programs where the patient has access to private and group counseling during and after the treatment period. Suboxone is a combined drug of buprenorphine and naloxone (see **Fig. 3**). Naloxone is an antagonist at μ receptors and is administered with buprenorphine to block its toxic effects in patients who try to inject suboxone intravenously as a drug of abuse. The antagonism is limited because the affinity of buprenorphine for the μ receptor is about 5 times that of naloxone.

Buprenorphine is also available as a transdermal patch (Butrans), is used to treat chronic, rather than acute, pain, and has been found to be effective for this purpose. However, the transdermal patch route has posed some challenges with regard to urine and oral drug testing because (1) it does not require the same first-pass metabolism through the liver as with sublingual (Subutex, Suboxon) ingestion and (2) releases micro doses compared with the pill form. Buprenorphine is metabolized via the CYP3A4 enzyme to norbuprenorphine via the liver and both analytes are often included in a standard urine drug test to demonstrate ingestion of the parent drug. The presence of both buprenorphine and its metabolite norbuprinorphine in the urine can help to obviate suspicion of diversion in a patient suspecting of adding straight buprenorphine directly to the urine, which would not yield norbuprinorphine in such a case.

Buprenorphine has been found to be more effective than methadone in treating patients with depressive traits,[32] a phenomenon that is thought to be associated with its pure antagonistic effects on κ receptors. Because it, like oxycodone, has become popular as a drug of abuse, screening for its presence in urine has become common. Toxic effects of this drug include nausea, vomiting, drowsiness, dizziness, headaches, memory loss, perspiration, dry mouth, miosis, orthostatic hypotension, impotence, decreased libido, and urinary retention. Constipation can occur, but is less frequent than with morphine. Hepatic necrosis and hepatitis with jaundice, as with the major tranquilizers/neuroleptic drugs, have further been observed in patients with high levels of buprenorphine. The half-life of buprenorphine is 23 to 42 hours, whereas that of naloxone is 2 to 12 hours. The detection window for urine drug testing for buprenorphine is 4 to 5 days and for naloxone it is approximately 2 days.

Fentanyl

This opiate analgesic (see **Fig. 3**), is about 80 times more potent than morphine in blocking pain. It can be taken orally as so-called fentanyl lollipops, smoked, inhaled, or administered by transdermal fentanyl patches.[29] Overdose effects of this drug are

the usual ones seen for opiate abuse and include respiratory depression and miosis. Treatment may involve irrigation of the bowel, and antiopiates such as naloxone may be administered. Hypotension is less common than with other opiates like morphine, because of the lack of histamine release. The detection window for fentanyl in urine is about 3 to 4 days after ingestion.

AMPHETAMINES

These compounds, as can be seen in **Fig. 5**, bear a close resemblance to the adrenergic amines such as epinephrine and norepinephrine, and may be expected to exert sympathomimetic effects. They also resemble dopamine and may be expected to have effects on dopaminergic pathways. The amphetamines cause euphoria and increased mental alertness that may be attributed to their effects on these pathways. This group of drugs, however, also exerts pronounced stimulatory

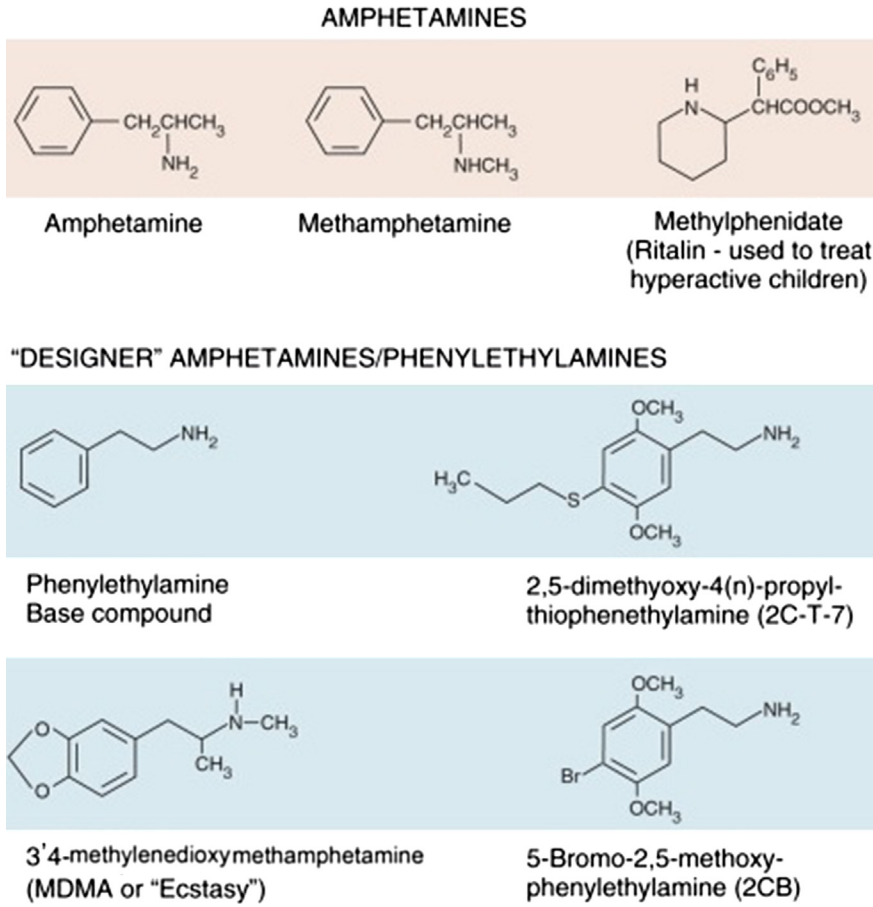

Fig. 5. Chemical structures of amphetamines and "designer" amphetamines/phenylethylamines. (*From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 332.e2; with permission.)

effects on γ- and β-receptors in the cardiovascular system and in the kidney to cause pronounced adrenergic effects such as increased heart rate, increased blood pressure, palpitations, bronchodilation, anxiety, pallor, and tremulousness. Studies indicate that amphetamines are also competitive inhibitors of the enzyme monoamine oxidase, which inactivates adrenergic neurotransmitters by oxidatively removing their amino groups. Blockage of this enzyme prolongs the effects of epinephrine and norepinephrine, with the attendant neurologic and cardiovascular sequelae.

One particular amphetamine, 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), a derivative of methamphetamine (see **Fig. 5**), has become popular as a recreational drug of abuse because it has euphoric and psychedelic effects but minimal hallucinogenic effects.[29] Various other methamphetamine derivatives (*N*-methyl-1-phenylpropan-2-amine) also referred to as Crystal Meth, Speed, Ice, and Chalk, among others, are continuously emerging as new drugs of abuse. Methamphetamine can be also be found in over-the-counter cold remedies and inhalers, which can cause confusion on drug testing.[33] However, in general, over-the-counter formulations contain the L-isomer [*R*(−)], which has mild dopaminergic effects and can be found in nasal decongestants (ie, Vicks VapoInhaler). In contrast, drugs containing the D-isomer [*S*(+)] (ie, Desoxyn used for attention deficit disorder) are strong CNS stimulants releasing dopamine from storage vesicles and interfering with dopamine transporter function, thereby affording high abuse liability owing to increased dopamine release in the extracellular synapse. Both Toxi-Lab (Irvine, CA) and enzyme-mediated immunologic technique (Syva, San Jose, CA) procedures are effective as a screening method in detecting these drugs of abuse. Occasionally, on the Toxi-Lab A strip, amphetamines may be confused with antihistamines like diphenhydramine. Confirmation of amphetamine and methamphetamine can be determined by GC/MS or LC/MS of patient's urine. When assessed by this method, methamphetamine and its D and L isomers have a detection window of approximately 2 to 3 days after ingestion. The presence of greater than 30% D isomer in the absence of prescription drugs that contain or metabolize to D-methamphetamine (Desoxyn, selegiline, benzphetamine) can raise suspicion of illicit drug use. Methamphetamine is converted to amphetamine, which has a detection window for urine drug testing of 3 to 5 days after ingestion.

The pharmacologic action of amphetamines includes CNS and respiratory stimulation and sympathomimetic activity (eg, bronchodilation, pressor response, mydriasis). Loss of weight may also occur as the result of an anorectic effect, which has been the reason for amphetamine and similar derivatives (ie, phentermine) for use and abuse in certain cases.[34] Psychic stimulation and excitability, leading to a temporary increase in mental and physical activity, can occur; anxiety and nervousness can also be produced.

Tolerance may be produced within a few weeks, and physical or psychological dependence may occur with prolonged use. Symptoms of chronic abuse include emotional lability, somnolence, loss of appetite, occupational deterioration, mental impairment, and social withdrawal. Trauma and ulcer of the tongue and lip may occur as a result of continuing chewing or teeth-grinding movements. A syndrome with the characteristics of paranoid schizophrenia can occur with prolonged use at a high dose. Aplastic anemia and fatal pancytopenia are rare complications.

No specific antidote for amphetamine overdose is known, and treatment of overdose is symptomatic with general physiologic supportive measures immediately implemented. When cardiovascular symptoms are noted, propranolol (Inderal) can be used as an antidote.

The quest for euphoria-producing drugs has resulted in the advent of synthetic phenylethylamines, so-called designer drugs, like MDMA, several further examples of which are shown in **Fig. 5**. With all of these drugs, the price for the sought-after effects of euphoria and hallucinations consists of headaches, nausea, vomiting, anxiety, agitation, violent behavior, tachycardia, hypertension, respiratory depression, and seizures, as discussed in the case of standard amphetamines.

Other phenylethylamine derivatives shown in **Fig. 5**, especially 2C-T-7 and 2CB, bind to 5-HT_2 receptors and induce hallucinogenic effects.[29] These drugs have been taken orally or have been insufflated, smoked, administered intravenously, and even taken rectally. Death from overdose of these designer drugs has been reported and varies based on newer compositions that become available over time. Unfortunately, thus far no specific assays are available for most of these drugs in urine. Their presence must be ascertained by history and/or symptoms reported in the absence of positive urine tests for standard amphetamines. On occasion, GC/MS LC/MS can be used to detect their presence.

TRYPTAMINES

Tryptamines are derivatives of serotonin, whose structure is shown in **Fig. 6**. These tryptamines, some of which occur in plants, are relatively simple to obtain and are also being assessed for select conditions (ie, xaliproden for chemotherapy-induced peripheral neuropathy). An example is *N,N*-dimethyltryptamine (DMT), which has strong hallucinogenic properties. Smoking DMT results in the rapid onset of hallucinogenic effects that are short-lived, giving rise to the term, "businessman's lunch." Other tryptamines contain modifications of the indole ring. These also allow them to interact with 5-HT receptors,[29] and this interaction is thought to result in their hallucinogenic effects. However, the mechanism of action of this class of drugs is not well understood. Psilocin shown in this figure is a component of the so-called Psilocybe, called magic mushrooms because of their hallucinogenic effects. The hallucinogenic effects of these drugs are enhanced by the presence of monoamine oxidase inhibitors such as β-carbolines. The mixture of these 2 compounds is present in a South American

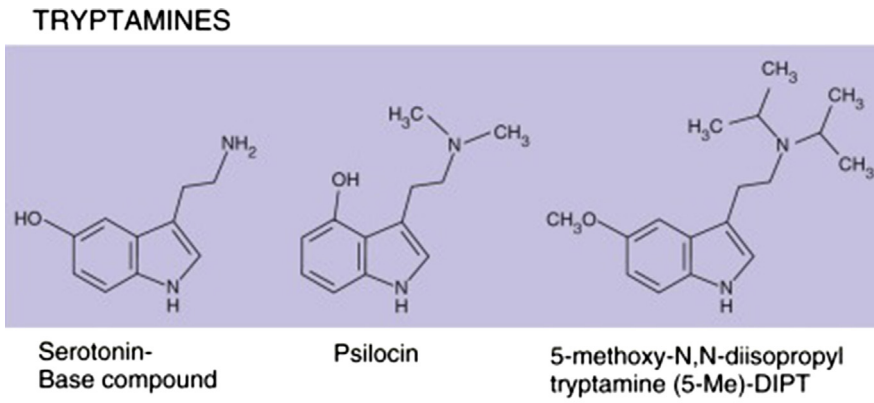

Fig. 6. Chemical structures of tryptamines. (*From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 333.e2; with permission.)

tea called *ayahuasca*, which combines 2 plants—one containing DMT and the other carbolines, which themselves can induce nausea and vomiting. Like the amphetamines and other phenylethylamine derivatives, the tryptamines cause, in addition to the "desired" effects of euphoria and empathy, auditory and visual hallucinations, nausea, vomiting, diarrhea, and emotional distress. Symptoms further include agitation, tachycardia, hypertension, diaphoresis, salivation, dystonia, mydriasis, tremors, confusion, seizures, and, in a few cases, rhabdomyolysis and paralysis. Currently, no routine assays are available for these compounds. As with the amphetamines, many of the psychogenic and physiologic effects of the tryptamines can be countered with supportive therapy and the administration of benzodiazepines.

PIPERAZINES

The structure of the parent compound, piperazine, is shown in **Fig. 7**. Several of the derivatives of piperazine are also shown. Many of these piperazines were used as antihelminthics during the 1950s, but were subsequently discontinued. However, their euphoria-producing effects were discovered, leading to a "legal" way of obtaining drugs of abuse. Two classes of piperazine derivatives have been identified: *N*-benzylpiperazines, the parent compound of which is *N*-benzylpiperazine (BZP), and phenylpiperazines. The former group includes 1-(3,4-methylenedioxybenzyl)piperazine, and the latter group includes 1-(3-chlorophenyl)piperazine, 1-(4-methoxyphenyl)piperazine, and 1-(3-trifluoromethylphenyl)piperazine (TFMPP). BZP (known as "A2") and TFMPP (known as "Molly") are among the most popular piperazines. Studies have shown that these piperazines produced effects that were similar to those of the amphetamines, suggesting that the target receptors of these drugs are the same. Both classes of piperazines have been found to increase dopamine and serotonin levels. TFMPP has been found to act as a partial agonist at 5-HT_{2A} receptors and

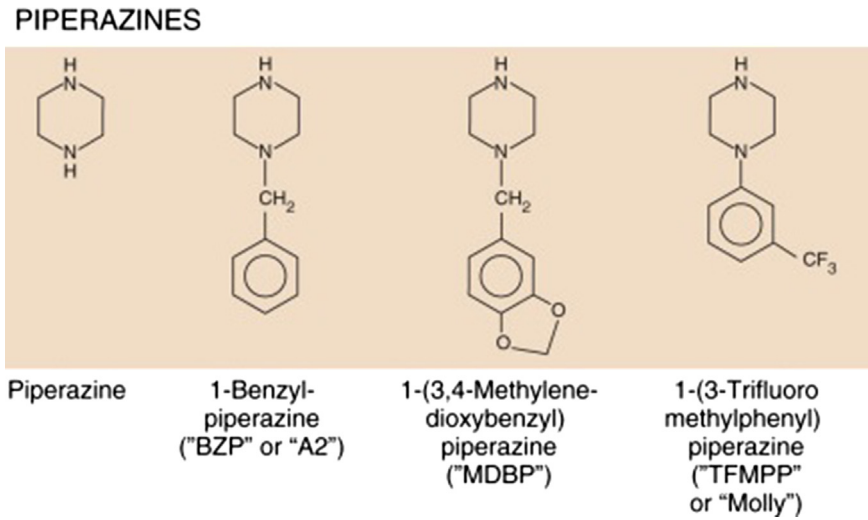

Fig. 7. Chemical structures of piperazines. (*From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 333.e2; with permission.)

is a full agonist at other 5-HT receptors. Although TFMPP is 3 times less potent than MDMA, it produces a full MDMA effect when combined with BZP, with which it is synergistic.[29] The TFMPP-BZP combination at low doses induces euphoria with decreased motor action, making the euphoric "experience" more pleasurable. The acute undesirable effects of piperazines are similar to those of the amphetamines and MDMA (ie, hallucinations, psychomotor agitation, increased heart rate and blood pressure, and increased body temperature). Deaths from BZP have been reported when combined with another drug like MDMA. Both TFMPP and BZP have skin irritant properties, causing sore nasal passages and throats; treatment is generally supportive. As with select tryptamines and designer amphetamines, currently no standard assay method detects these drugs in urine, although recent methods to detect these drugs using LC/MS have been described.[35]

BENZODIAZEPINES

Among this group of drugs, shown in **Fig. 8**, the most prominent is diazepam (Valium); they are used therapeutically, as so-called minor tranquilizers. Their mechanisms of action seem to be potentiation of GABA, a neurotransmitter that inhibits conduction in dopaminergic neurons, and facilitation of its binding to GABA receptors.[36] Benzodiazepines bind to the α subunit of the $GABA_A$ receptor at a site that is distinct from that for GABA itself and cause an increase in the frequency of chloride ion channel opening at the $GABA_A$ receptor. Usually used as a therapeutic drug to produce calming effects at doses between 2.5 and 10 mg and to produce muscle-relaxing effects at higher doses, diazepam has been used by drug addicts in high dosage to counter the excitatory effects of other drugs of abuse or as a means of inducing tranquil states. Among some drug abusers, benzodiazepines are used to potentiate the effects of heroin.[37] A number of drug abusers have become addicted to diazepam when using high doses several times each day. Acutely, benzodiazepine overdose may produce somnolence, confusion, seizures, and coma. Rarely, hypotension, respiratory depression, and cardiac arrest may occur. Chronically, physical and psychological dependence occur. Sudden discontinuance of the drug may lead to anxiety, sweating, irritability, hallucinations, diarrhea, and seizures. Treatment is supportive. Gradual diminution of the benzodiazepine removes physical dependence. The half-life for diazepam is 20 to 70 hours, but the half-life of one of its active metabolites is 50 to 100 hours. Other common benzodiazepines include alprazolam (Xanax) and lorazepam (Ativan), which differ in the half-life and are often administered based on clinical needs (ie, alprazolam for panic disorder) and dosing. Many benzodiazepines can be detected in urine directly as the parent drug or as selective metabolites. For example, diazepam can be detected via its metabolites of nordiazepam and temazepam, both of which catabolize to oxazepam; alprazolam can be detected by its active metabolite α-hydroxyalprazolam (see **Fig. 8**). In general, the detection window for urine sampling after ingestion is approximately 5 to 7 days after ingestion or 6 weeks with chronic ingestion (>1 year of use). Recent studies have reported greater ease and speed of sample extraction methods thereby affording a broader range of compounds that can be analyzed with shorter run times using LC/MS technology.[38]

PHENCYCLIDINE

This interesting tricyclic compound, shown in **Fig. 9**, has numerous effects on a variety of different neural pathways. Used almost exclusively as a drug of abuse, this

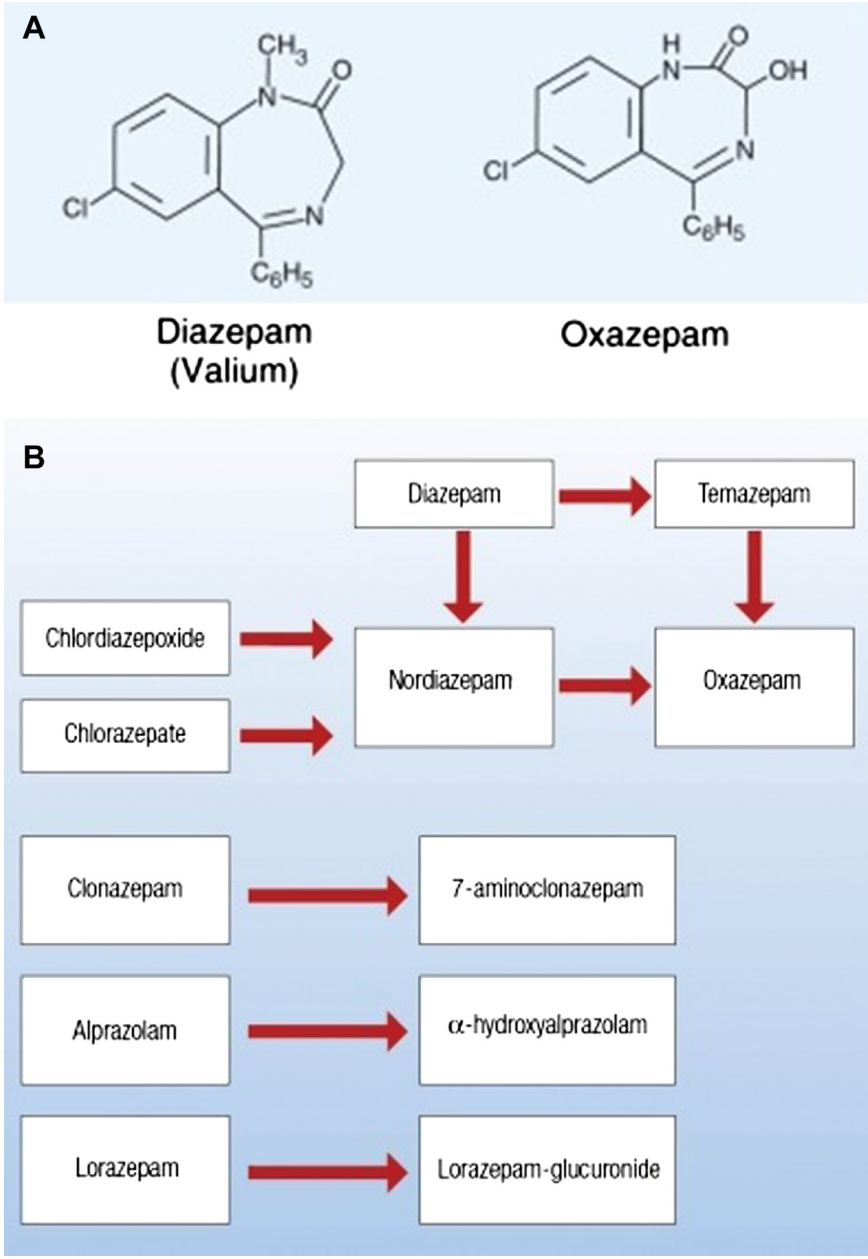

Fig. 8. (*A*) Chemical structures of benzodiazepines. (*B*) Benzodiazepine metabolic pathways. (*From* [*A*] *From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 331.e2, with permission; and [*B*] *Reprinted with* permission from Pract Pain Manage 2014;14(1):38–41. © 2016 Vertical Health Media, LLC.)

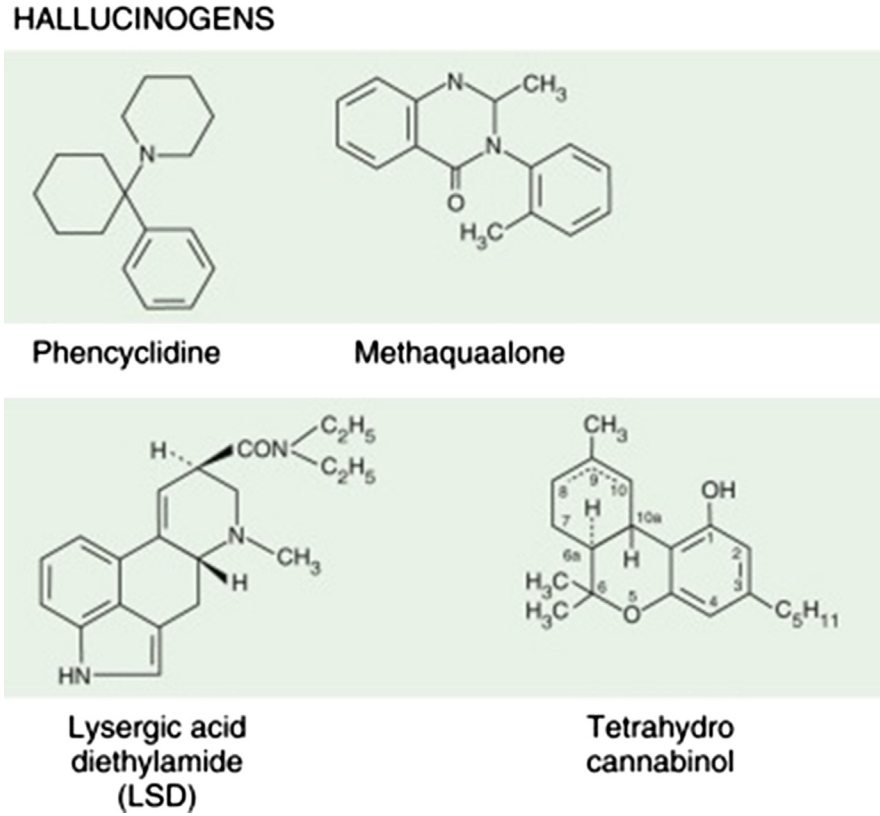

Fig. 9. Chemical structures of hallucinogens. (*From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 332.e2; with permission.)

drug is traded on the streets under the name of *angel dust* or *angel hair*. It is peculiar that the use of this drug seems to be periodic. The physiologic effects of PCP seem to be analgesic and anesthetic and, paradoxically, stimulatory. This drug has been found to interact with cholinergic, adrenergic, GABA-secreting, serotonergic, and opiate neuronal receptors. As with ketamine, PCP has also been found to block NMDA receptors with slight variations.[39] Thus, a wide variety of bizarre and apparently paradoxic symptoms can be seen in the same patient. This drug has been shown to bind to specific regions of the inner chloride channels of neurons, apparently profoundly affecting chloride transport. It has also been found to bind strongly to a class of neural receptors referred to as sigma-receptors.[40] This type of receptor binds strongly to the neuroleptic, antipsychotic drug haloperidol (Haldol)—a finding that may implicate the sigma-receptor in some of the clinical findings of severe psychosis in patients suffering from overdose with PCP.

Because of its varied actions, clinically acute manifestations vary from depression to euphoria and can involve catatonia, violence, rage, and auditory and visual hallucinations. Vomiting, hyperventilation, tachycardia, shivering, seizures, coma, and death are among the common occurrences that result from abuse of this drug. Most fatalities

occur from the hypertensive effects of the drug, especially on the large cerebral arteries. As can be inferred from this spectrum of possible symptoms, diagnosis based on clinical findings alone can be quite challenging. Only the results of a drug screen and/or urine drug confirmation studies can be diagnostic. The general detection window in urine can be 5 to 7 days after ingestion and even longer (approximately 30 days) with heavy use. Treatment of drug abuse with PCP is supportive, with the patient kept in isolation in a darkened, quiet room. Acidification of the urine increases the rate of PCP excretion. As might be expected from findings regarding the sigma-receptor, treatment with haloperidol results in sedation of the violent, hallucinating patient.

BARBITURATES

An almost bewildering variety of these major sedative drugs is available. However, all are derivatives of barbituric acid, which may be regarded as the condensation product of urea and malonic acid, as indicated in **Fig. 10**. Depending on the substituents of the $-CH_2$ group of the malonic acid portion, the particular drug may be long acting, as is phenobarbital, with a benzene ring and ethyl group substituents on this carbon; short acting, as is pentobarbital, with neopentyl and ethyl groups at this position; or ultrashort acting, as is the case with thiopental. The long-acting barbiturate phenobarbital is a therapeutic drug that is used as an anticonvulsant, unlike the

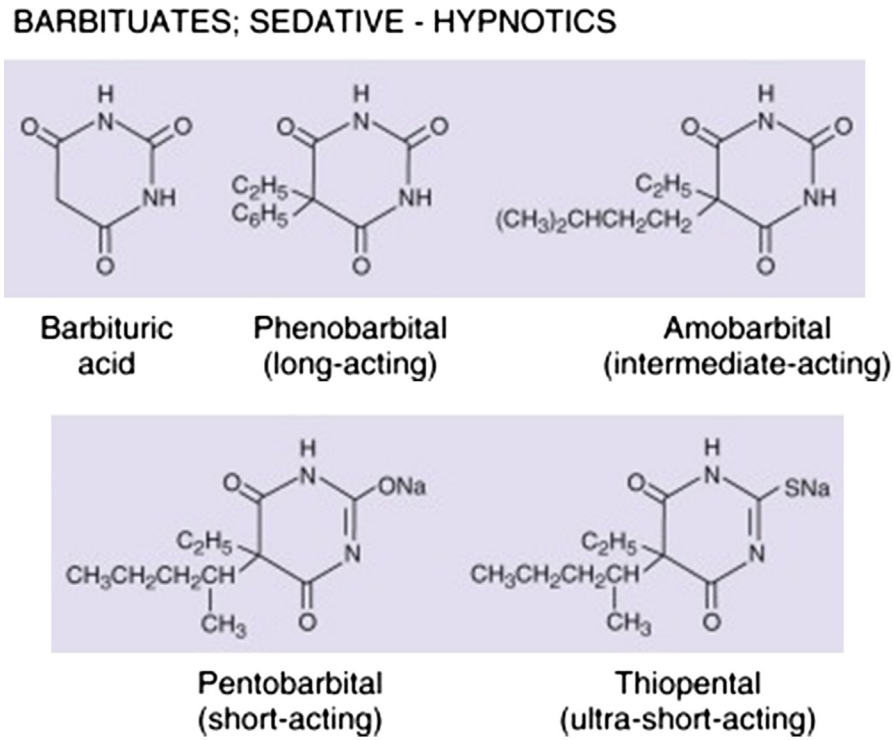

Fig. 10. Chemical structures of barbiturates and sedative–hypnotics. (*From* Pincus MR, Bluth MH, Abraham NZ. Toxicology and therapeutic drug monitoring. In: Pincus MR, McPherson RA, editors. Henry's clinical diagnosis and management by laboratory methods. 23rd edition. Elsevier; 2017. p. 331.e2; with permission.)

short- and ultrashort-acting drugs. All of the barbiturates are fat soluble and therefore pass easily across the blood–brain barrier. All of them seem to stabilize membranes such that depolarization of the membranes becomes more difficult.

As with the benzodiazepines, the barbiturates are known to interact with GABA receptors. In particular, they bind to the α subunit of the $GABA_A$ receptor at a site that is distinct both from the GABA binding site and from the benzodiazepine binding site. Their effect is to increase the duration of chloride ion channel opening at the $GABA_A$ receptor, potentiating the GABA effect (ie, inhibition of dopamine-dependent nerve conduction). It is thought that this action of chloride channel opening, called direct gating of the chloride channel, is the basis for barbiturate toxicity, which is greater than for the benzodiazepines, which do not increase the duration of chloride channel opening but rather increase the frequency of channel opening. In addition, at higher doses, barbiturates have been found to inhibit a subtype of glutamate receptors, called AMPA receptors. Glutamate is a major excitatory neurotransmitter. More generally, barbiturates have been found to block calcium ion–induced release of neurotransmitters.[41]

For unknown reasons, the short-acting and ultrashort-acting barbiturates seem to inhibit selectively the reticular activating system, involved with arousal—hence their sedative and hypnotic effects. The ultrashort-acting barbiturates rapidly diffuse out of the CNS, accounting for their rapid action. Phenobarbital, however, selectively reduces the excitability of rapidly firing neurons and is therefore a highly effective anticonvulsant. It may be more than coincidence that phenobarbital and the equally effective anticonvulsant phenytoin (Dilantin) bear structural resemblance to one another and may exert similar effects on rapidly firing neurons.

Clinically, at low doses, the short-acting and ultrashort-acting barbiturates produce sedation, drowsiness, and sleep. They also impair judgment. At higher doses, anesthesia is produced. At very high doses, these drugs can cause stupor, coma, and death. The toxic manifestations of these drugs are depression, Cheyne-Stokes respiration, cyanosis, hypothermia, hypotension, tachycardia, areflexia, and pupillary constriction. Treatment of drug overdose is supportive and includes the standard treatment for shock. When administered within 30 minutes of drug ingestion, activated charcoal is an effective barbiturate chemoadsorbent.

Diagnosis of drug abuse with short- and ultrashort-acting barbiturates is done by immunoassay and TLC screening procedures. High-performance liquid chromatography has found some use in this regard, but is not a standard method. Immunoassays for those drugs are also excellent, the one caveat being that high levels of phenobarbital in urine cross-react with antibodies against the short-acting barbiturates. Additionally, confirmatory urine toxicology testing has a detection window of 2 days and greater than 3 weeks for long-acting formulations after ingestion of barbiturates in general.

PROPOXYPHENE

Although withdrawn from the US market in 2010, this analgesic drug, whose structure is shown in **Fig. 3**, has pharmacologic properties very similar to those of the opiates, like morphine. As can be seen in the figure, the structure of propoxyphene (Darvon) is quite similar to that of methadone. This drug can be taken orally, so that the sedated, good feelings induced by opiates can be induced without the need to have recourse to the intravenous apparatus needed for infusion of heroin. A major cause of drug-related death is propoxyphene overdose alone or in combination with CNS depressants like barbiturates and alcohol. Toxic symptoms are similar to those seen with overdoses

of opiates (namely, respiratory depression, cardiac arrhythmias, seizures, pulmonary edema, and coma). Nephrogenic diabetes insipidus may also occur. In addition, propoxyphene has been found to cause cardiac arrhythmias.[42] Treatment for propoxyphene overdose is mainly supportive. Administration of naloxone reverses the toxic effect of the drug. Urine confirmatory testing (ie, LC/MS) has a detection window of 2 to 3 days after ingestion and can be used to differentiate propoxyphene from other opiates.

METHAQUALONE (QUAALUDE)

Methaqualone is a 2,3-disubstituted quinazoline (see **Fig. 9**). Although not structurally similar to the barbiturates, it has many of the same sedative–hypnotic properties as the barbiturates. This compound also possesses anticonvulsant, antispasmodic, local anesthetic, antitussive, and weak antihistamine actions. Oral administration leads to rapid and complete absorption of the drug, with approximately 80% bound to plasma protein. Peak plasma concentrations are reached in approximately 2 to 3 hours, and almost all of the drug seems to be metabolized by the hepatic cytochrome P450 microsomal enzyme system, with only a small percentage (<5%) excreted unchanged in the urine. The serum half-life ranges from 20 to 60 hours. The dosages used for its hypnotic–sedative actions range from 150 to 300 mg daily. Toxic serum concentrations are generally reached at 10 μg/mL. Tolerance to some of its actions, as well as dependence, occurs, such that abusive dosages can be up to 6 to 7 times greater than those used therapeutically. Symptoms of overdose can be similar to barbiturate toxicity and produce CNS depression with lethargy, respiratory depression, coma, and death. However, unlike barbiturate overdose, muscle spasms, convulsions, and pyramidal signs (hypertonicity, hyperreflexia, and myoclonus) can result from severe methaqualone intoxication. Treatment for overdose includes supportive therapy, as well as delaying absorption of remaining drug with activated charcoal and drug removal by gastric lavage.

MARIJUANA (CANNABIS)

This is one of the oldest and most widely used of the mind-altering drugs. Marijuana is a mixture of cut, dried, and ground portions of the hemp plant *Cannabis sativa*. Hashish refers to a more potent product produced by extraction of the resin from the plant. The principal psychoactive agent in marijuana is considered to be δ-9-tetrahydrocannabinol (δ-9-THC; see **Fig. 9**), a lipid-soluble compound that readily enters the brain and may act by producing cell membrane changes. δ-9-THC binds to the presynaptic neural cannabinoid receptor CB1, which releases the inhibitory neurotransmitter GABA in the hippocampus, amygdala, and cerebral cortex. Different forms of THC have been found to cause distinctly different physiologic effects.[43] δ-9-THC induces an increase in anxiogenic effects, and cannabidiol produces a diminution in anxiety. The latter derivative was found to attenuate blood oxygenation levels in the amygdala and the anterior and posterior cingulate cortex; δ-9-THC was found to modulate activation in frontal and parietal regions of the brain.

Marijuana may be introduced through the lungs by smoking or through the GI tract by oral ingestion in food. Once THC enters the body, it is readily stored in body fat and has a half-life of approximately 1 week. Biotransformation is complex and extensive, and less than 1% of a dose is excreted unchanged. About one-third is excreted in the urine, primarily as δ-9-carboxy-THC and 11-hydroxy-δ-9-THC. These metabolites may be detected in the urine from 1 to 4 weeks after the last ingestion, depending on both dosage and frequency of ingestion.

Marijuana does not seem, in general, to cause physiologic dependence, but tolerance and psychological dependence do seem to occur, and a proportion of chronic users of this drug can develop physiologic dependence. Two major physiologic effects of marijuana are reddening of the conjunctivae and increased pulse rate. Muscle weakness and deterioration in motor coordination can also occur. The preponderant changes seen with cannabis intoxication are perceptual and psychic changes. These range from euphoria, relaxation, passiveness, and altered time perception, seen at low doses, to adverse reactions such as paranoia, delusions, and disorientation, which can be seen at high doses in psychologically susceptible individuals.

The dosage, the route of administration, the individual's psychological makeup, and the setting are important determinants in each individual's reaction to cannabis intoxication. Thus, high doses in an individual unprepared or unaware of drug consumption may produce a disturbing experience. More commonly, experienced users report mild euphoria, enhancement or alteration of the physical senses, introspection with altered emphasis or importance of ideas, and heightening of subjective experiences. Heavy chronic use may produce bronchopulmonary disorders; although the relative safety of chronic use is controversial, acute panic reactions, delirium, and psychoses occur rarely. Few users seek treatment, and when this occurs in a distressed patient, medical intervention is generally conservative. However, after an acute episode, psychological evaluation may be necessary in an individual with an underlying psychiatric disturbance. Rarely, marijuana may be ingested by intravenous infusion of a boiled concentrate. Severe multisystem toxicity may be produced by this route of administration. Symptoms may include acute renal failure, gastroenteritis, hepatitis, anemia, and thrombocytopenia.

LYSERGIC ACID DIETHYLAMIDE (LYSERGIDE)

Lysergic acid diethylamide (LSD; see **Fig. 9**) is a semisynthetic indolalkylamine and a hallucinogen. It is one of the most potent pharmacologic materials known, producing effects at doses as low as 20 μg, and is equally effective by injection or oral administration. Comparison of the structure of LSD with that of 5-hydroxytryptamine (serotonin), as shown in the group 6 drugs in **Fig. 9**, reveals that LSD has a tryptaminelike nucleus, but it lacks the 5-hydroxyl group of serotonin. LSD has multiple complex effects in the CNS. In the locus coeruleus and the median raphe of the midbrain, which use serotonergic pathways, it has the paradoxic effect of inhibiting both the firing of neurons in these structures and the release of serotonin at the axonal sides of synapses.[44] This process, in turn, may produce a state of CNS hyperarousal. In contrast, it actually acts as a serotonin agonist on postsynaptic HT_{1A} receptors. It is a pure agonist on 5-HT_2 receptors in other serotonergic pathways. Recently, it has been found that the hallucinogenic effect of LSD is owing to its agonistic effect on 5-HT_2 receptors, and that it behaves very much like the tryptamines (see **Fig. 6**) and phenylethylamines (see **Fig. 5**), discussed previously, in producing this effect. In addition, it has been found to have both agonistic and antagonistic effects on dopaminergic pathways. Thus, it acts at multiple sites in the CNS in complex ways. LSD further affects both the sympathetic and parasympathetic nervous systems. However, the sympathetic effect seems to be greater, and initial symptoms include hypertension, tachycardia, mydriasis, and piloerection.

The usual dosage of LSD is 1 to 2 μg/kg; LSD produces an experience that begins within an hour of ingestion, usually peaks at 2 to 3 hours, and generally lasts 8 to

12 hours, after ingestion. Metabolism occurs in the liver, whereas excretion occurs mainly in the bile. The detection window in urine is 1 to 2 days after ingestion.

LSD is the most commonly abused drug in its class and is believed by its users to provide insights and new ways of solving problems. The psychological effects are usually intense and vary, depending on the user's personality, expectations, and circumstances. LSD acts on all body senses, but visual effects are most intense. Common perceptual abnormalities include changes in the sense of time, organized visual illusions or hallucinations, blurred or undulating vision, and synesthesias. Mood may become very labile, and dissolution and detachment of ego may occur. LSD toxicity levels are low, and deaths are generally owing to trauma secondary to errors in the user's judgment. Panic reactions—a bad trip—are the most common adverse reactions. These may occur in any user and cannot be reliably predicted or prevented. Borderline psychotic and depressed individuals are at risk for the precipitation of suicide or a prolonged psychotic episode by the usage of LSD. Flashbacks, which are poorly understood, occur days to months after ingestion. This occurs when the user experiences recurrences of a previous hallucinogenic experience in the absence of drug ingestion. Acute panic reactions may be treated by frequent reassurance and a quiet and calm environment; diazepam may also be effective. However, except for treating specific complications, LSD abuse has no systematic program of treatment.

CATHINONES (BATH SALTS)

Synthetic cathinones (ie, "bath salts"; **Fig. 11**) are a type of psychoactive designer drug that produce amphetaminelike or cocainelike subjective effects by activating monoamine systems in the brain and periphery.[45] Bath salts produce the expected desirable effects at lower doses. However, high doses as well as chronic exposure can foster psychosis, violent behaviors, tachycardia, hyperthermia, and even death. There are 3 main synthetic cathinones: 4-methyl-*N*-methylcathinone (mephedrone),

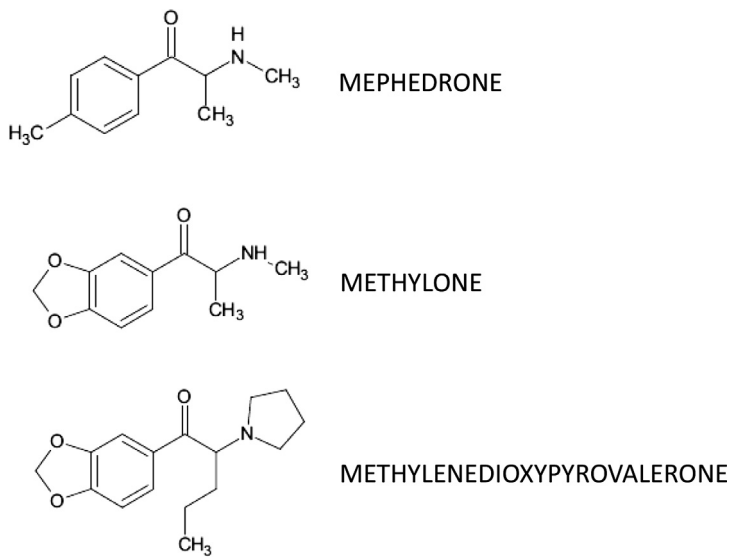

Fig. 11. Chemical structures of bath salts.

3,4-methylenedioxy-*N*-methylcathinone (methylone), and 3,4-methylenedioxypyrovalerone. These compounds are structurally related to the parent compound cathinone, which is a naturally occurring β-keto amphetamine with known psychostimulant properties. Bath salts enhance sympathetic nervous system activity and are thought to act by increasing the concentration of dopamine in the synaptic cleft that results in increased activation of postsynaptic dopamine receptors (see **Fig. 1**). Furthermore bath salts such as methcathinone is a substrate for the dopamine transporter, thereby blocking the ability of dopamine to bind to the transporter and subsequently reducing one of the main mechanisms of dopaminergic neurotransmission termination.

The diagnosis of bath salt ingestion requires a high index of suspicion when evaluating a patient presenting with intoxication or overdose, because there are no commonly available laboratory drug screening testing approaches that can be used at a point of care or office setting at the time of presentation. They may precipitate a false-positive methamphetamine drug screening result. Laboratory detection of synthetic cathinones requires high complexity GC/MS or LC/MS confirmatory testing with a detection window for urine sample of 2 to 3 days after ingestion. Serum and urine toxicologic studies can also identify potential coingestion of other toxic agents. Treatment of synthetic cathinone overdose is primarily supportive care as a specific antidote does not exist. The most common treatments used in emergency departments are intravenous fluids, benzodiazepines, oxygen, and sedatives. Specific metabolic sequelae (hyponatremia, myocarditis, and necrotizing fasciitis) should be treated by medical and/or surgical interventions as required.[46]

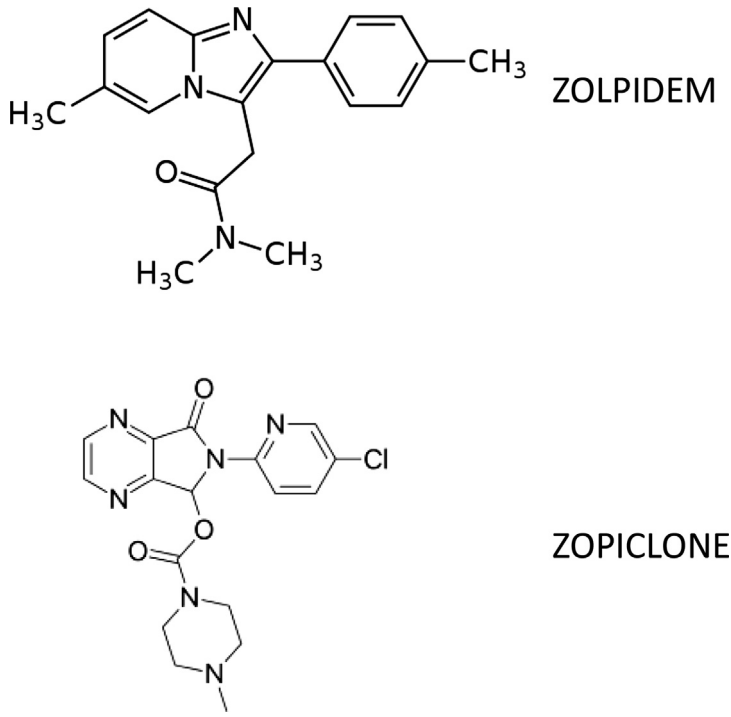

Fig. 12. Chemical structures of sleep aids.

SLEEP AIDS

It is estimated that 1 in 6 adults with a diagnosed sleep disorder and 1 in 8 adults with trouble sleeping reported using sleep aids, that 50 to 70 million Americans suffer from sleep disorders or deprivation and that 4% of adults aged 20 and over reported using a prescription sleep aid in the past month, with greater use in the elderly.[47] Furthermore, sleep aids include sedative/hypnotic agents and are also subject to dependency and abuse. Prescription sleep aids include barbiturates and benzodiazepine in addition to other agents. The imidazopyridine zolpidem (Ambien), represents a chemically novel nonbenzodiazepine hypnotic agent (**Fig. 12**), which binds to the ω-1 receptor in the brain. Unlike benzodiazepines, zolpidem does not contain myorelaxant or anticonvulsant effects and its effects on anxiety seem to be minor. It does not seem to affect sleep stages, but does seem to reduce the latency to and prolongs the duration of sleep in patients with insomnia owing to its rapid onset of action and short elimination half-life.[48] In contrast, the cyclopyrrolone zopiclone/eszopiclone (Lunesta), another nonbenzodiazepine hypnotic agent (see **Fig. 12**), modulates the $GABA_A$ receptor through allosteric mechanisms.[49] Although its receptor binding is not facilitated directly by GABA, its interaction with the $GABA_A$ receptor can potentiate responses to GABA. As such, coadministration of benzodiazepines, which is not uncommon in those with sleep disorders, can have deleterious potentiating effects. The detection window for these sleep aids are generally 1 to 7 days after ingestion when conventionally assessed via GC/MS or LC/MS confirmatory testing approaches.

MUSCLE RELAXANTS

Pain management of musculoskeletal conditions include carisoprodol (ie, Soma; **Fig. 13**), a CNS depressant with an unknown mechanism of pharmacologic action. Its sedative effects are generally attributed to the actions of its primary metabolite, meprobamate, at $GABA_A$ receptors. Interestingly, although its primary metabolite meprobamate (ie, Miltown, Equanil; see **Fig. 13**) is classified as a controlled substance at the federal level, carisoprodol is not.[50] These agents are available in varying doses and ingestion recommendations and the general detection window in a urine sample after ingestion is 1 to 3 days. There have been reports of carisoprodol-related abuse,

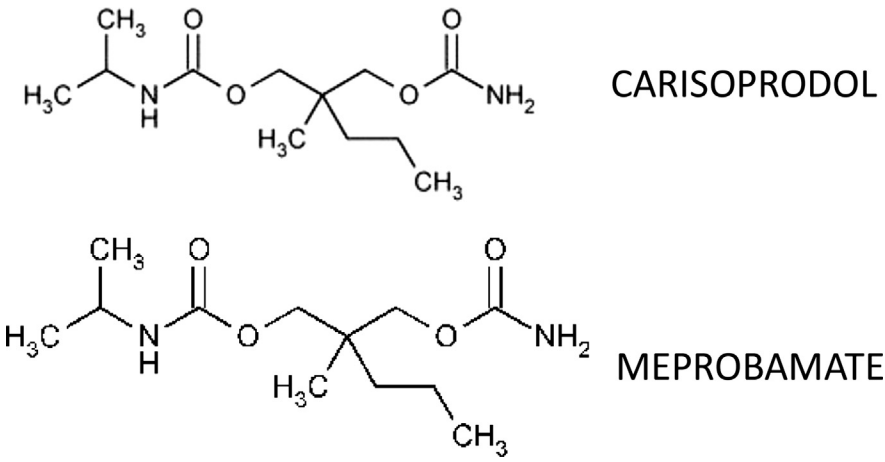

Fig. 13. Chemical structures of muscle relaxants: carisoprodol and meprobamate.

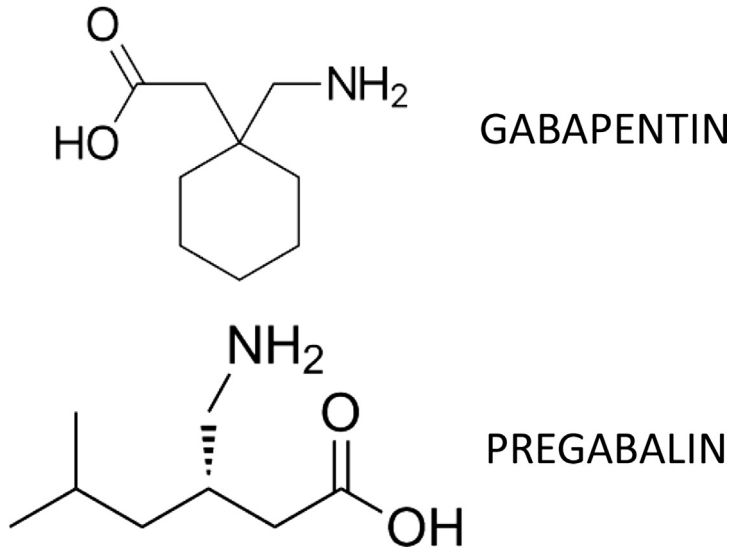

Fig. 14. Chemical structures of muscle relaxants: gabapentin and pregabalin.

diversion, and death thus deeming it a drug of concern for the US Department of Justice Drug Enforcement Agency Office of Diversion Control. In Florida, the number of carisoprodol/meprobamate–related deaths in 2005 exceeded those attributed to opioids, including heroin and fentanyl. Thus, abuse of carisoprodol has become an international problem. Recently, the Committee for Medicinal Products for Human Use concluded the abuse potential associated with carisoprodol outweighs its benefits as a therapeutic drug.

ANTIEPILEPTICS

Gabapentin (ie, Neurontin), a 3-alkylated analog of GABA, and pregabalin (Lyrica; Fig. 14) are commonly prescribed agents used to treat epilepsy. Other applications of these drugs include neuropathic pain, fibromyalgia, and possibly for treating postoperative pain. In addition gabapentin has been considered effective for the treatment of restless leg syndrome, Guillain–Barré syndrome, uremic pruritus, and phantom limb pain, whereas pregabalin has also been considered effective for the treatment of generalized anxiety disorder.[51] The mechanism of action is thought to include the activity as a ligand at the alpha2-delta subunit of voltage-gated calcium channels by calcium influx at nerve terminals. This interaction reduces the release of neurotransmitters, such as glutamate norepinephrine and substance P. To this end, gabapentin has recently been reported to facilitate cannabis abstinence by producing effects that overlap with those of cannabinoids[52] and recent animal studies show synergistic pain reduction effects when coadministered with morphine and its metabolites.[53] This has propagated abuse potential both in synergy with other agents to potentiate their effects as well as for this drug class in its own right.[54] The general detection window (urine) for gabapentin and pregabalin is 1 to 4 days after ingestion.

OTHER DRUGS

There is no lack of ingenuity when it comes to conjuring up new synthetics. There have been a number of new synthetic cannabinoids available to the clinical marketplace,

many of which have deleterious health effects that are more severe than that of marijuana. These have brand names like "Spice" or "K2," among other, and their effects can be physical and affect cardiovascular, neurologic, renal, pulmonary, metabolic, or psychological and can also affect cognitive and behavioral functions, among others.[55] These synthetic cannabinoids, propagated by "street" chemists, can be of the benzoyl, naphthoyl, alkoyl, and phenylacetyl derivatives among others and comprise greater than 50 different types.[56] For example, the aminoalkylindole cannababinoid derivative JWH-018 (1-penthyl-3-(1-napthoyl)indole), one of the first derivatives detected in K2 preparations seized in the United States, is thought to exert its effects via G protein coupled cannabanoid type 1 (CB-1) receptors. The affinity of JWH-018 for the CB-1 receptor is about 15 times greater than conventional Δ^9-THC. Although the general detection window for urine testing is about 3 to 5 days after ingestion of JWH-018 and similar analogs, there are no quality control and manufacturing standards for such illicit substances.

SUMMARY

The management of pain is an ever evolving discipline. New formulations of narcotic analgesics mature to the marketplace in a timely fashion with the promises of availing improved pain control, better dosing, fewer side effects, and the like. These agents also avail an equal risk for abuse, which may mature as a result of physiologic tolerance, polypharmacy, metabolic factors, phramacogenomics, and economic concerns among others. Street chemists are equally adept at both manipulating current and evolving drugs to more potent versions in addition to creating new compositions of matter for consumption in the medical and illicit marketplaces. Although the clinical assessment of the patient is paramount to developing an index of suspicion of overdose, toxicity or illicit drug use, the clinical laboratory can provide a unique and valuable resource to support such investigations and guide appropriate therapy. As new agents pervade the health care system so too does the clinical toxicology laboratory keep in step with adapting its technology and methodology to facilitate detection of such substances.

REFERENCES

1. Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality. Results from the 2014 national survey on drug use and health: detailed tables. Rockville (MD): SAMHSA. Available at: http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.pdf. Accessed April 15, 2016.
2. Meyer MR, Maurer HH. Absorption, distribution, metabolism and excretion pharmacogenomics of drugs of abuse. Pharmacogenomics 2011;12:215–33.
3. Smith ML, Hughes RO, Levine B, et al. Forensic drug testing for opiates. VI. Urine testing for hydromorphone, hydrocodone, oxymorphone, and oxycodone with commercial opiate immunoassays and gas chromatography-mass spectrometry. J Anal Toxicol 1995;19:18–26.
4. Vadivelu N, Lumermann L, Zhu R, et al. Pain control in the presence of drug addiction. Curr Pain Headache Rep 2016;20:35.
5. Knittel JL, Holler JM, Chmiel JD, et al. Analysis of parent synthetic cannabinoids in blood and urinary metabolites by liquid chromatography tandem mass spectrometry. J Anal Toxicol 2016;40:173–86.
6. Tsai IL, Weng TI, Tseng YJ, et al. Screening and confirmation of 62 drugs of abuse and metabolites in urine by ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry. J Anal Toxicol 2013;37:642–51.

7. Manchikanti L, Malla Y, Wargo BW, et al. Comparative evaluation of the accuracy of benzodiazepine testing in chronic pain patients utilizing immunoassay with liquid chromatography tandem mass spectrometry (LC/MS/MS) of urine drug testing. Pain Physician 2011;14:259–70.
8. Blum K, Chen AL, Giordano J, et al. The addictive brain: all roads lead to dopamine. J Psychoactive Drugs 2012;44:134–43.
9. Hurd YL, Kehr J, Ungerstedt U. In vivo microdialysis as a technique to monitor drug transport: correlation of extracellular cocaine levels and dopamine outflow in the rat brain. J Neurochem 1988;51:1314–6.
10. Baldessarini RJ. Drug therapy of depression and anxiety disorders. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 11th edition. New York: McGraw-Hill; 2006. p. 429–59.
11. Kablinger AS, Lindner MA, Casso S, et al. Effects of the combination of metyrapone and oxazepam on cocaine craving and cocaine taking: a double-blind, randomized, placebo-controlled pilot study. J Psychopharmacol 2012;26:973–81.
12. Li P, Eaton MM, Steinbach JH, et al. The benzodiazepine diazepam potentiates responses of α1β2γ2L γ-aminobutyric acid type A receptors activated by either γ-aminobutyric acid or allosteric agonists. Anesthesiology 2013;118:1417–25.
13. Fujii H, Narita M, Mizoquchi M, et al. Drug design and synthesis of epsilon opioid receptor agonist: 17-(cyclopropylmethyl)-4,5alpha-epoxy-3,6beta-dihydroxy-6,14-endoethenomorphinan-7alpha-(N-methyl-N-phenethyl)carboxamide (TAN-821) inducing antinociception mediated by putative epsilon opioid receptor. Bioorg Med Chem 2004;12:4133–45.
14. Zhuo M. Plasticity of NMDA receptor NR2B subunit in memory and chronic pain. Mol Brain 2009;2:1–11.
15. Gonzalez J, Tukey RH. Drug metabolism. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 11th edition. New York: McGraw-Hill; 2006. p. 71–91.
16. Smith HS. Opioid metabolism. Mayo Clin Proc 2009;84:613–24.
17. Dwyer JP, Jayasekera C, Nicoll A. Analgesia for the cirrhotic patient: a literature review and recommendations. J Gastroenterol Hepatol 2014;29:1356–60.
18. Jones JH, Wie WB. Cocaine-induced chest pain. Clin Lab Med 2006;26:127–46.
19. Hoffman RS. Cocaine. In: Flomenbaum NE, Goldfrank LR, Hoffman RF, et al, editors. Goldfrank's toxicologic emergencies. 8th edition. New York: McGraw-Hill; 2006. p. 1133–47.
20. Azmitia EC, Murphy RB, Whitaker-Azmitia PM. MDMA (ecstasy) effects on cultured serotonergic neurons: evidence for Ca2+-dependent toxicity linked to release. Brain Res 1990;510:97–103.
21. Cami J, Farre M. Drug addiction. N Engl J Med 2003;349:975–86.
22. Forray A, Foster D. Substance use in the perinatal period. Curr Psychiatry Rep 2015;17:91.
23. Tso PH, Wong YH. Molecular basis of opioid dependence: role of signal regulation by G-proteins. Clin Exp Pharmacol Physiol 2003;30:307–16.
24. von Euler M, Villén T, Svensson JO, et al. Interpretation of the presence of 6-monoacetylmorphine in the absence of morphine-3-glucuronide in urine samples: evidence of heroin abuse. Ther Drug Monit 2003;25:645–8.
25. Smith ML, Nichols DC, Underwood P, et al. Morphine and codeine concentrations in human urine following controlled poppy seeds administration of known opiate content. Forensic Sci Int 2014;241:87–90.

26. Chen P, Braithwarte RA, George C, et al. The poppy seed defense: a novel solution. Drug Test Anal 2014;6:194–201.
27. Bell J, Seres V, Bowron P, et al. The use of serum methadone levels in patients receiving methadone maintenance. Clin Pharmacol Ther 1988;43:623–9.
28. Diong SH, Mohd Yusoff NS, Sim MS, et al. Quantitation of methadone and metabolite in patients under maintenance treatment. J Anal Toxicol 2014;38:660–6.
29. Haroz R, Greenberg MI. New drugs of abuse in North America. Clin Lab Med 2006;26:147–64.
30. Schier J. Avoid unfavorable consequences: dextromethorphan can bring about a false-positive phencyclidine urine drug screen. J Emerg Med 2000;18:379–81.
31. Smith MT. Differences between and combinations of opioids re-visited. Curr Opin Anaesthesiol 2008;21:596–601.
32. Gerra G, Borella F, Zaimovic A, et al. Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. Drug Alcohol Depend 2004;75:37–45.
33. Smith ML, Nichols DC, Underwood P, et al. Methamphetamine and amphetamine isomer concentrations in human urine following controlled Vicks VapoInhaler administration. J Anal Toxicol 2014;38:524–7.
34. Haslam D. Weight management in obesity - past and present. Int J Clin Pract 2016;70:206–17.
35. Montesano C, Sergi M, Moro M, et al. Screening of methylenedioxyamphetamine- and piperazine-derived designer drugs in urine by LC-MS/MS using neutral loss and precursor ion scan. J Mass Spectrom 2013;48:49–59.
36. Campo-Soria C, Chang Y, Weiss DS. Mechanism of action of benzodiazepines on $GABA_A$ receptors. Br J Pharmacol 2006;148:984–90.
37. Fraser AD. Use and abuse of the benzodiazepines. Ther Drug Monit 1998;20:481–9.
38. Perez ER, Knapp JA, Horn CK, et al. Comparison of LC-MS-MS and GC-MS analysis of benzodiazepine compounds included in the drug demand reduction urinalysis program. J Anal Toxicol 2016;40:201–7.
39. Hevers W, Hadley SH, Luddens H, et al. Ketamine, but not phencyclidine, selectively modulates cerebellar $GABA_A$ receptors containing $\alpha 6$ and δ subunits. J Neurosci 2008;28:5383–93.
40. Skuza G. Pharmacology of sigma (σ) receptor ligands from a behavioral perspective. Curr Pharm Des 2012;18:863–74.
41. Löscher W, Rogawski MA. How theories evolved concerning the mechanism of action of barbiturates. Epilepsia 2012;53:12–25.
42. Barkin RL, Barkin SJ, Barkin DS. Propoxyphene (dextropropoxyphene): a critical review of a weak opioid analgesic that should remain in antiquity. Am J Ther 2006;13:534–42.
43. Fusar-Poli P, Crippa JA, Bhattacharyya S, et al. Distinct effects of Δ9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry 2009;66:95–105.
44. Passie T, Halpern JH, Stichtinoth DO, et al. The pharmacology of lysergic acid diethylamide: a review. CNS Neurosci Ther 2008;14:295–314.
45. Banks ML, Worst TJ, Rusyniak DE, et al. Synthetic cathinones ("bath salts"). J Emerg Med 2014;46:632–42.
46. Thornton MD, Baum CR. Bath salts and other emerging toxins. Pediatr Emerg Care 2014;30:47–52.
47. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. Prescription sleep aid use among adults: United States 2005-2010.

Atlanta (GA): CDC; 2013. Available at: http://www.cdc.gov/nchs/products/databriefs/db127.htm.
48. Langtry HD, Benfield P. Zolpidem. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 1990;40:291–313.
49. Döble A, Canton T, Malgouris C, et al. The mechanism of action of zopiclone. Eur Psychiatry 1995;10:117s–28s.
50. Gonzalez LA, Gatch MB, Forster MJ, et al. Abuse potential of soma: the GABA(A) receptor as a target. Mol Cell Pharmacol 2009;1:180–6.
51. Calandre EP, Rico-Villademoros F, Slim M. Alpha2delta ligands, gabapentin, PGB and MGB: a review of their clinical pharmacology and therapeutic use. Expert Rev Neurother 2016. [Epub ahead of print].
52. Lile JA, Wesley MJ, Kelly TH, et al. Separate and combined effects of gabapentin and [INCREMENT]9-tetrahydrocannabinol in humans discriminating [INCREMENT] 9-tetrahydrocannabinol. Behav Pharmacol 2016;27:215–24.
53. Papathanasiou T, Juul RV, Gabel-Jensen C, et al. Population pharmacokinetic modelling of morphine, gabapentin and their combination in the rat. Pharm Res 2016. [Epub ahead of print].
54. Bossard JB, Ponté C, Dupouy J, et al. Disproportionality analysis for the assessment of abuse and dependence potential of pregabalin in the French Pharmacovigilance Database. Clin Drug Investig 2016;36(9):735–42.
55. Castellanos D, Gralnik LM. Synthetic cannabinoids 2015: an update for pediatricians in clinical practice. World J Clin Pediatr 2016;5:16–24.
56. Debruyne D, Le Boisselier R. Emerging drugs of abuse: current perspectives on synthetic cannabinoids. Subst Abuse Rehabil 2015;6:113–29.