Newly Emerging Drugs of Abuse

Kenichi Tamama and Michael J. Lynch

Contents

Kenichi Tamama and Michael J. Lynch contributed equally to this work.

K. Tamama (✉)
Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Clinical Laboratories, University of Pittsburgh Medical Center Presbyterian Hospital, Pittsburgh, PA, USA

McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Clinical Laboratory, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA
e-mail: tamamakj@upmc.edu

M. J. Lynch (✉)
Division of Medical Toxicology, Department of Emergency Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Pittsburgh Poison Center, Pittsburgh, PA, USA
e-mail: lyncmj@upmc.edu

Handbook of Experimental Pharmacology, https://doi.org/10.1007/164_2019_260

Abstract

Drug use and the associated overdose deaths have been a serious public health threat in the United States and the world. While traditional drugs of abuse such as cocaine remain popular, recreational use of newer synthetic drugs has continued to increase, but the prevalence of use is likely underestimated. In this review, epidemiology, chemistry, pharmacophysiology, clinical effects, laboratory detection, and clinical treatment are discussed for newly emerging drugs of abuse in the following classes: (1) opioids (e.g., fentanyl, fentanyl analogues, and mitragynine), (2) cannabinoids [THC and its analogues, alkylindole (e.g., JWH-018, JWH-073), cyclohexylphenol (e.g., CP-47,497), and indazole carboxamide (e.g., FUB-AMB, ADB-FUBINACA)], (3) stimulants and hallucinogens [β-keto amphetamines (e.g., methcathinone, methylone), pyrrolidinophenones (e.g., α-PVP, MDPV), and dimethoxyphenethylamine ("2C" and "NBOMe")], (4) dissociative agents (e.g., 3-MeO-PCP, methoxetamine, 2-oxo-PCE), and (5) sedative-hypnotics (e.g., gabapentin, baclofen, clonazolam, etizolam). It is critically important to coordinate hospital, medical examiner, and law enforcement personnel with laboratory services to respond to these emerging threats.

Keywords

Cannabinoids · Dissociative agent · Drug abuse · Opioids · Sedative-hypnotic · Stimulant

1 Introduction

The world has witnessed a consistent and accelerating rise in overdose deaths for the past 40 years (Jalal et al. 2018). A variety of drug classes have contributed to patterns of recreational use, misuse, addiction, overdose, and death. Over the last two decades, opioids have dominated attention given the unprecedented contribution of this class of drugs to individual and cultural harm in addition to overdose deaths. The overdose death rate tripled from 1999 to 2016 with more than 70,000 overdose deaths reported in 2017, the majority of which were opioid related (Hedegaard et al. 2017; National Institute on Drug Abuse (NIDA) 2018). Nonfatal and fatal overdoses, particularly involving heroin and prescription opioids as well as cocaine, increased worldwide between 1980 and 2013 (Martins et al. 2015). The landscape of drug use has shifted throughout that period within the opioid class of drugs. Beginning in the late 1990s and through the first decade of this century, prescription opioids were the primary cause of overdose mortality with annual overdose deaths exceeding deaths from motor vehicle collisions in 2008. In 2010–2012, opioid prescribing peaked and began to decline in the United States (Guy et al. 2017). At the same time, the cost of high purity heroin was low (Drug Enforcement Administration (DEA) 2017). Overdose death rates from heroin rose precipitously. Then, in 2014, fentanyl and associated analogues began to enter the illicit heroin market, primarily from illicit manufacturers and distributors in China and Mexico (Drug Enforcement Administration (DEA) 2018a). Due to the potency of these drugs and the insidious nature of their introduction to the illicit opioid market, overdose deaths from fentanyl and related synthetic opioids rapidly became the leading cause of unintentional overdose deaths in the years following widespread availability (National Institute on Drug Abuse (NIDA) 2018). Despite the prevalence of fentanyl related compounds and their devastating toll, identification of continuously evolving analogues has proven challenging. Coordination of hospital, medical examiner, and law enforcement personnel with laboratory services has become increasingly important as we continue to respond to this threat (Daniulaityte et al. 2017).

With increasing attention and targeted intervention, prescription opioid and illicit opioid use has declined. However, non-opioid drug use has increased (Substance Abuse and Mental Health Services Administration (SAMHSA) 2018). The classes of illicit drugs available for use have not changed significantly for decades. Classes include stimulants, cannabinoids, sedative-hypnotics, and dissociative agents. However, the specific drugs within these categories have evolved in both receptor specificity and potency leading to an ever-changing landscape of novel psychoactive substances (NPS). Traditional drugs including cocaine, amphetamines, methamphetamines, cannabis, and phencyclidine remain popular. Deaths associated with cocaine and methamphetamine have risen significantly since 2014 (National Institute on Drug Abuse (NIDA) 2018). However, the availability and use of newer synthetic drugs have continued to increase (Drug Enforcement Administration (DEA) 2018a). Due to the influx of newer drugs and variable chemical composition, prevalence of use is likely underestimated given the difficulty in identification

and the transient presence of individual drugs within a drug class. Moreover, combinations of drugs such as cocaine adulterated with fentanyl or inclusion of synthetic cannabinoids with fentanyl products have led to unintended and mixed toxicity further complicating clinical management and laboratory identification.

Substance use and associated toxicity have been a continuous phenomena in the United States for decades. The deaths of tens of thousands of Americans per year, primarily from opioid toxicity, have drawn sharp attention to the issues of substance use and addiction. Past experience demonstrates that while the drug of choice will change over time, drug use will continue to be a critical focus of public health and law enforcement policy. Recently, the variety of available drugs has expanded significantly beyond the traditional drugs of just a decade ago. A summary of emerging drugs is presented in Table 1. In order to properly respond to this changing environment, accurate identification of a wide spectrum of drugs will be necessary (Table 2).

2 Opioids

2.1 Epidemiology

Opioid use and misuse have expanded dramatically since the late 1980s–early 1990s. Poorly treated pain as well as a misunderstanding of the potential adverse effects of long-term opioid use combined with pharmaceutical company and regulatory pressures to adequately relieve pain led to marked increases in opioid prescribing from the 1990s through 2010 (Jones et al. 2018). As opioid prescribing began to decline in 2010–2012, illicit use of heroin and then fentanyl rose precipitously (Hedegaard et al. 2017). Starting in 2014, fentanyl and its analogues infiltrated the illicit opioid market. Deaths related to illicitly manufactured fentanyl and associated analogues rose 88% from 2013 to 2016 and rapidly became the most common cause of unintentional overdose death in the United States (Hedegaard et al. 2017). In 2017, 16 fentanyl-related compounds and potent non-fentanyl synthetic opioids like U-47700 were identified in drug seizures by DEA in addition to pure fentanyl (Drug Enforcement Administration (DEA) 2018b). In the first half of 2018, fentanyl accounted for ~75% of opioid identifications by the DEA and was mixed with heroin in 48% of its identifications indicating the significant prevalence of fentanyl in the drug supply as well as the potential for inadvertent use of fentanyl products (Drug Enforcement Administration (DEA) 2018c). Since 2012, 28 new fentanyl analogues have been identified in the European Union, with 18 of them being identified for the first time in 2016–2017. It is important to note that seized products have included pills pressed to look like prescription pharmaceuticals, nasal sprays, and vaping liquids. Seventy percent of European opioid seizures in 2016 were fentanyl and associated analogues (European Monitoring Centre for Drugs and Drug Addiction 2018). The economic burden of the opioid crisis in the United States has been estimated at $78.5 billion/year for prescription opioids alone and at more than $500 billion in 2015 when considering all opioids (Florence et al. 2016). In 2017, the opioid crisis was declared a

Table 1 Examples of emerging drugs of abuse by category. Derived from Drug Enforcement Administration (DEA) (2017)

Opioids	Stimulants	Cannabinoids	Dissociative agents	Sedative-hypnotics
Benzoylbenzyl fentanyl	N-Ethylbuphedrone	FUB-PB-22	3-Methoxy-phencyclidine	Phenazepam
2-Thifuranyl fentanyl	Methylone	5F-EMB-PINACA	Methoxetamine	Diclazepam
U-48800	4-Methylenedioxy-α-pyrrolidinobutiophenone	5F-AB-PINACA	Methoxphenidine	Flubromazolam
Benzylfentanyl	4-Methylethylaminopentiophenone	SDB-005	Deschloroketamine	Flubromazepam
U-49900	α-Pyrrolidinohexanophenone	NM2201	2-Oxo-PCE	Etizolam
Tetrahydrofuran fentanyl	Ethylone	MDMB-CHMICA	Dextromethorphan	Clonazolam
3-Methylfentanyl	Pentylone	5F-AKB48		
Butyryl fentanyl	α-Pyrrolidinovalerophenone	AB-PINACA		
Acryl fentanyl	4-Chloroethcathinone	5F-AMB		
Methoxyacetylfentanyl	Dibutylone	ADB-CHMINACA		
Cyclopropylfentanyl	N-Ethylpentylone	5F-UR-144		
Acetylfentanyl	25I-NBOMe	AB-FUBINACA		
Carfentany78l	25C-NBOMe	MMB-CHMICA		
4-Fluoroisobutyryl fentanyl	4-Bromo-2,5-dimethoxyphenethylamine	ADB-FUBINACA		
U-47700	4-Hydroxy-N-methyl-N-ethyltryptamine	5F-MDMB-PINACA		
Furanyl fentanyl	5-Methoxy-N,N-dimethyltryptamine	FUB-AMB		
Mitragynine	4-Acetoxy-N,N-dimethyltryptamine			
Salvinorin				
Ibogaine				

Table 2 Summary of classes of emerging drugs of abuse including mechanism of action, clinical effects, laboratory testing techniques, and treatment

Drug class	Pharmacology of toxicity	Clinical effects	Laboratory testing	Treatment
Opioids	μ-Opioid receptor agonism (major); δ- and κ-opioid receptor agonism (minor)	Sedation, miosis, respiratory depression	FDA-cleared immunoassays available for opiates, 6-MAM, and fentanyl	Assisted ventilation; titrated naloxone dosing
Synthetic cannabinoids	Potent CB1 receptor agonism; CB2 agonism less clinically relevant for acute toxicity	Paranoia, agitation, tachycardia, hypertension, vomiting	No FDA-cleared immunoassays available	$GABA_A$-agonist sedation (benzodiazepines or barbiturates)
Stimulants and hallucinogens	Norepinephrine, dopamine, and serotonin reuptake inhibition and receptor agonism	Hallucinations, agitation, delirium, seizures, tachycardia, hypertension	Partially cross-reactive with FDA-cleared amphetamine immunoassays	$GABA_A$-agonist sedation (benzodiazepines or barbiturates); dopamine antagonists (antipsychotics)
Dissociative agents	Glutamate NMDA-receptor antagonism	Nystagmus, dissociation, tachycardia, occasionally agitation	Partially cross-reactive with FDA-cleared PCP immunoassays	$GABA_A$-agonist sedation (benzodiazepines or barbiturates)
Sedative-hypnotics	$GABA_A$ and $GABA_B$ receptor agonism	Sedation, hyporeflexia; tachycardia and myoclonus with $GABA_B$ agonists	FDA-cleared immunoassays available for benzodiazepines, but not for GABA derivatives	Supportive care with airway protection if needed; flumazenil in selected scenarios

public health emergency. Given the profound impact opioids have had on medical practice and society in the United States, thorough evaluation and understanding of the effects of these drugs and accurate identification and surveillance are critical (O'Donnell et al. 2017).

2.2 Chemistry and Chemical Structures

Opiates, such as morphine, are opium poppy *Papaver somniferum*-derived psychoactive alkaloids consumed by human beings since the ancient Mesopotamia era circa 3,400 BC (Presley and Lindsley 2018). Opiates have the pentacyclic phenanthrene ring structure (Fig. 1). The major psychoactive alkaloid included in opium poppy is morphine, which is also a direct precursor of heroin. Heroin is 3,6-diacetylmorphine that was pharmaceutically developed by diacetylation of morphine by Bayer in 1898 as a nonaddictive morphine derivative, but it turned out to be strongly addictive. Thebaine, another opiate and biosynthetic precursor to morphine, is chemically modified to develop naloxone (Fig. 1) (Devereaux et al. 2018).

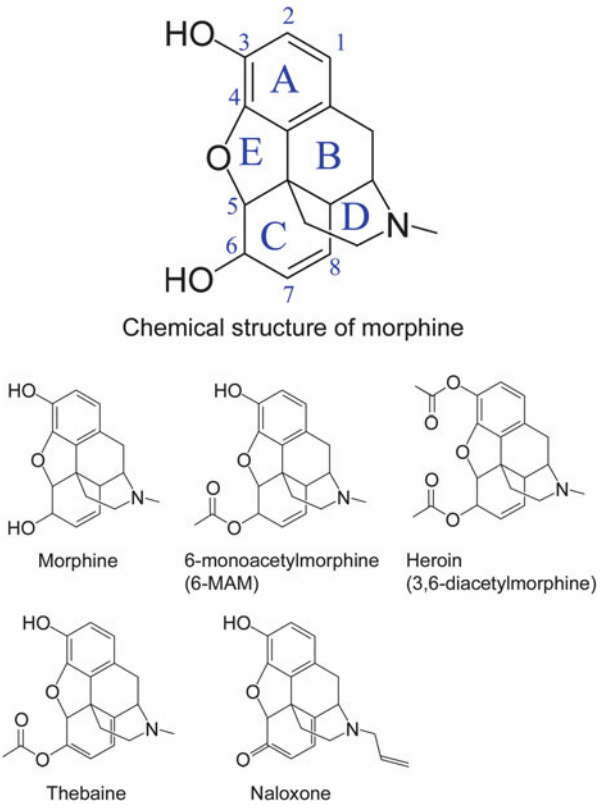

Fig. 1 Chemical structures of morphine and structurally related compounds. The pentacyclic phenanthrene ring structure (ring A–E) and numbering of morphine are also provided in the figure

Fentanyl was first developed by Dr. Paul Janssen, the founder of Janssen Pharmaceuticals and innovative scientist, who developed more than 80 drugs in 1960. He hypothesized that a piperidine ring is the most important chemical structure of morphine and meperidine in their analgesic effect; indeed, fentanyl was synthesized as a piperidine-derivative analgesic and anesthetic agent (Domino 2008; Stanley 1992; Stanley et al. 2008).

Fentanyl and its analogues are synthetic phenylpiperidine or 4-anilidopiperidine opioids (Vuckovic et al. 2009), and its chemical structure substantially differs from that of opiates, even though fentanyl and opiates share the piperidine ring. The fentanyl skeleton consists of N-alkyl chain, piperidine ring, amide group, and aniline ring (Cayman Chemical 2018). Various fentanyl analogues have been developed through substitution of these moieties (Fig. 2).

Nomenclature of these fentanyl analogues is confusing. Typically, the name of the chemical moiety substituting the ethyl or ethoxy moiety in the amide group in fentanyl is added in front of "fentanyl." For example, an ethoxy moiety is replaced with the acetyl moiety in acetylfentanyl, whereas an ethyl moiety is replaced with the butyryl moiety in butyrylfentanyl. Chemical modification can be made in other groups as well. For example, a methyl group is attached to the 3-position in the piperidine ring in 3-methylfentanyl, whereas a carbomethoxy group is attached to the 4-position in the piperidine ring in 4-carbomethoxy fentanyl or carfentanil. A fluorine atom is attached to the *para*-position in the aniline ring in para-fluorobutyrylfentanyl and para-fluoroisobutyrylfentanyl.

There are other classes of synthetic opioids. U-47700 was developed by a pharmaceutical company Upjohn in the 1970s as a more potent opioid analgesic (Szmuszkovicz 1976). It is a structural isomer of AH-7921, a synthetic analgesic with cyclohexylmethylbenzamide structure (Fig. 3) (Brittain et al. 1973).

Mitragynine is a major alkaloid included in the plant *Mitragyna speciosa*, also known as kratom, indigenous to Southeast Asia (Jansen and Prast 1988). 7-Hydroxy mitragynine is a minor alkaloid in kratom, but it is a more potent opioid than mitragynine (Takayama et al. 2002). Both mitragynine and 7-hydroxy mitragynine are classified as monoterpenoid indole alkaloids. These compounds also do not have a piperidine ring in their structure (Fig. 3).

2.3 Pharmacology and Physiology Overview

Opioid receptors exist throughout the CNS including the brain and spinal cord. Traditionally, μ-, δ-, and κ-receptors have been described and studied with subtypes of each and a fourth, nociceptin opioid receptor (NOP), receiving more recent attention due to its distinct endogenous ligand-binding affinity relative to the other opioid receptors (Shang and Filizola 2015). Each type of opioid receptor plays a role in analgesia through a variety of peripheral, spinal, and cerebral activities. The μ-opioid receptor has most typically been targeted as a potent analgesic but is also responsible for undesired adverse effects (Ling et al. 1985). The κ- and δ-receptors appear to contribute to spinal and supraspinal analgesia and represent targets of

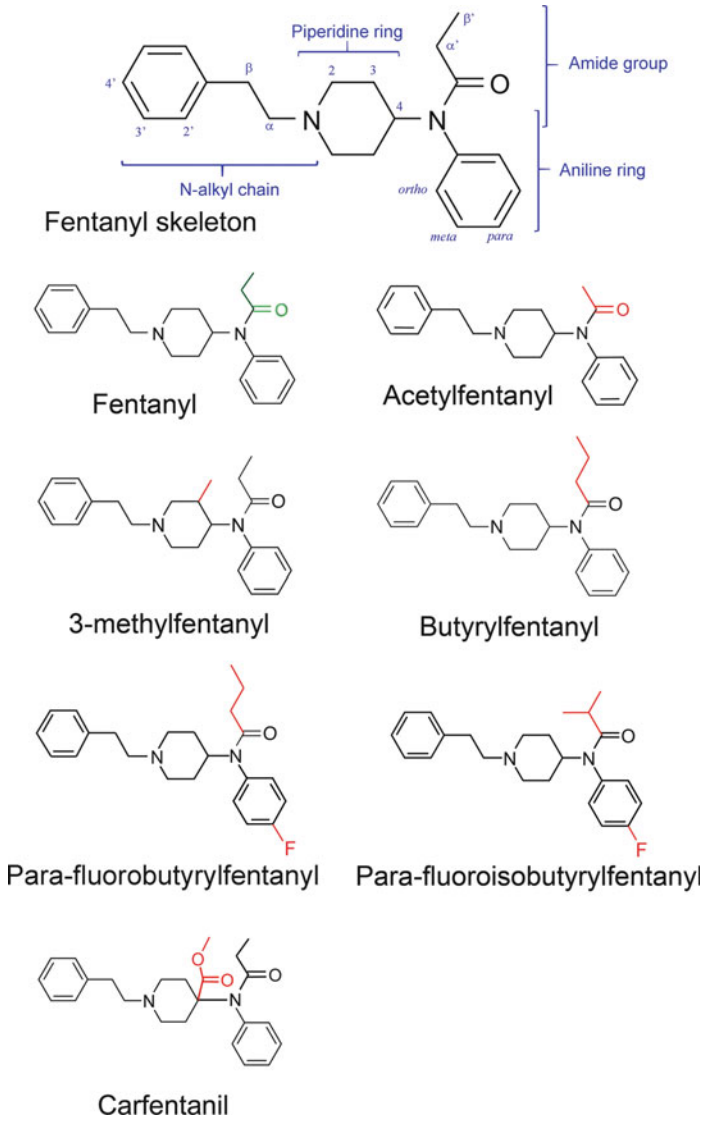

Fig. 2 Chemical structures of fentanyl and fentanyl analogues. The chemical structure of the fentanyl skeleton is also provided. The ethoxy moiety of fentanyl is highlighted in green. The substituting moiety in each fentanyl analogue is highlighted in red

ongoing investigation for therapeutic investigation as well as recreational use, e.g., salvinorin and ibogaine (Gendron et al. 2016; Listos et al. 2011; Litjens and Brunt 2016; Roach and Shenvi 2018). Mitragynine and 7-hydroxy mitragynine, found in kratom, are partial μ-opioid receptor agonists as well as κ- and δ-opioid receptor antagonists. Adrenergic and dopaminergic receptor activation is also described

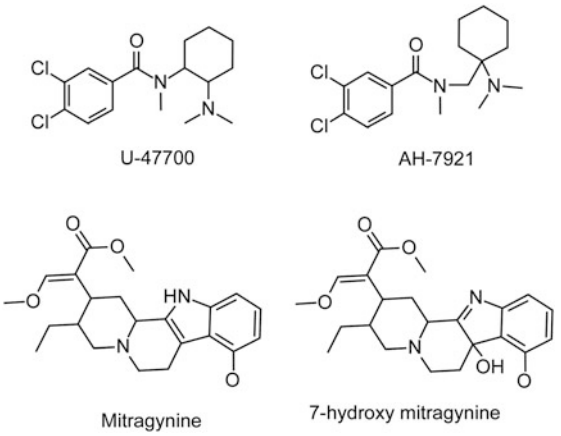

Fig. 3 Chemical structures of U-47700, AH-7921, mitragynine, and 7-hydoxy mitragynine

which results in stimulant properties at lower doses with opioid predominance at higher doses (Kruegel and Grundmann 2018). Naloxone, a μ-receptor antagonist, does not reverse the effects of κ- or δ-opioid receptor activity, and agonists at those sites do not cause respiratory depression.

Time to onset of peak effect and potency of various opioids is conferred by a combination of structural specificity for the opioid receptor as well as capacity to enter the CNS rapidly. For instance, the synthetic opioid class of 4-anilidopiperidine which includes fentanyl and its analogues provides much more potent stimulus of the opioid receptor. Fentanyl is estimated to be 50–100 times as potent as morphine (Vuckovic et al. 2009). Within that class of drugs, variable potency can be seen with relatively minor changes in chemistry. 4-Carbomethoxy fentanyl, or carfentanil (Fig. 2), for example, is approximately 20–30 times as potent as fentanyl and is responsible for deaths throughout the world (Armenian et al. 2018; European Monitoring Centre for Drugs and Drug Addiction 2018; Vuckovic et al. 2009). Heroin results in more rapid onset of euphoria compared to morphine due to its lipophilic addition of two acetyl groups accelerating delivery of morphine to the CNS opioid receptors (Maas et al. 2018). The metabolite, 6-monoacetylmorphine (6-MAM), is nearly pathognomonic for heroin exposure as morphine is not naturally acetylated in the human body (Maas et al. 2018).

Some opioids confer pharmacologic effects other than pure opioid receptor agonism. Serotonin receptor activation secondary to reuptake inhibition has been demonstrated with opioids including tramadol, meperidine, dextromethorphan/dextrorphan, and fentanyl (Baldo 2018). Delayed repolarization of cardiac myocytes with associated QT interval prolongation and risk of polymorphic ventricular tachycardia can be seen with methadone, ibogaine, and loperamide (Behzadi et al. 2018). In addition to serotonin reuptake inhibition, blockade of norepinephrine reuptake by meperidine, tramadol, and their metabolites can result in seizures (Hassamal et al. 2018).

Finally, a variety of adulterating agents have been identified in illicit opioids which may lead to mixed pharmacology and clinical effects. Opioids and other illicit

drugs typically are mixed with other compounds which may simply be diluents or bulking agents, e.g., sugars, to deliver a certain weight while minimizing the amount of valuable drug that is included. Adulterants are pharmacologically active constituents that are intentionally included for a variety of reasons that may include enhancing the effect, mitigating associated adverse drug effects, or simply as a lower cost substitute for the primary drug (United Nations Office for Drug Control and Crime Prevention (UNODCCP) 2001). Contaminants, on the other hand, are substances which were not intentionally included and can include bacterial toxins such as botulinum which has been reported worldwide (MacDonald et al. 2013; Palmateer et al. 2013; Yuan et al. 2011). Pharmacologically active adulterants vary significantly by time and geography. However, reported heroin adulterants have included paracetamol/acetaminophen, diphenhydramine, clenbuterol, lidocaine, xylazine, caffeine, diphenhydramine (aka "cheese"), phenobarbital, griseofulvin, diazepam, procaine, quinine/quinidine, chloroquine, methaqualone, and dextromethorphan (Broseus et al. 2016; Phillips et al. 2012; Ruiz-Colon et al. 2014; Solimini et al. 2017). Depending upon the presence and relative concentration of an adulterant, significant clinical effects may manifest that complicate and/or cloud the presentation of a patient with acute opioid intoxication.

2.4 Clinical Effects

Therapeutic use of opioids results in desired effects including potent and rapid reduction in pain as well as cough suppression. However, the distribution and activity of primarily μ-opioid receptors in the medullary respiratory center and gastrointestinal tract result in adverse effects and toxicity at supratherapeutic doses (Minami and Satoh 1995). Additionally, indirect activation of mesolimbic dopamine reward centers and intrinsically rewarding euphoric effects of opioids result in habituation and addiction (Kreek et al. 2012). Opioid use results in constipation with both short- and long-term use (Webster 2015). Acute opioid toxicity includes a typical triad of clinical signs: sedation or coma, hypoventilation, and miosis. Additional toxicity may include seizures, cardiac dysrhythmias, and serotonergic effects depending upon individual drug pharmacology. The onset of respiratory depression and arrest can be rapid, within minutes (Boom et al. 2012). Early signs of respiratory depression are typically hypercapnia followed by hypoxemia meaning that declines in oxygen saturation on pulse oximetry are a later finding. Cyanosis, bluish discoloration of the lips and distal extremities, is a clinical indicator of respiratory failure. Miosis may not be present with some opioids, particularly tramadol and meperidine with concurrent serotonin- and norepinephrine-mediated toxicity. While opioids exert myocardial depressant effects as well as histamine-mediated vasodilation resulting in hypotension, cardiovascular toxicity is primarily the result of hypoxemia and hypoperfusion secondary to respiratory failure. As respiratory failure progresses, secondary cardiac failure and arrest can occur. Pulmonary edema is frequently noted on postmortem examinations as well as in patients who have survived an overdose. There is a reported association of development of pulmonary edema following rapid

reversal of acute toxicity with naloxone, but it is unclear if naloxone contributes to this process through catecholamine surge versus unmasking of developing pulmonary edema as part of the natural course of opioid toxicity, sudden inspiration against a closed glottis, or a combination of these factors (Megarbane and Chevillard 2013). Aspiration pneumonitis and pneumonia also frequently complicate opioid toxicity with mental status depression particularly in the presence of vomiting (Table 2).

2.5 Laboratory Detection and Methodology

Laboratory tests used in the clinical laboratories are subject to the law and regulations in each country. In the United States, FDA clearance is required before an immunoassay kit is used in clinical laboratories unless laboratory-developed tests under the Clinical Laboratory Improvement Amendments (CLIA) regulation (Genzen et al. 2017). FDA-cleared opiate immunoassays are included in routine urine drug screening panels. Opiate immunoassays cross-reacts with morphine, 6-MAM, and heroin, but not naloxone, unless its concentration is extremely high (Straseski et al. 2010). As 6-MAM is the immediate metabolite of heroin and morphine is the metabolite of 6-MAM, heroin abuse can be screened by opiate immunoassays, even though the half-life of heroin and 6-MAM is very short in the blood (less than 10 min and 40 min, respectively) (Goldberger et al. 1993). FDA-cleared 6-MAM immunoassays, such as Syva® EMIT® II Plus 6-Acetylmorphine kit (Siemens), are also available, allowing for the rapid screening of previous heroin usage with better specificity to 6-MAM than opiate immunoassays, but the positive results are regarded as "Presumptive" or "Unconfirmed" positive, and MS-based confirmatory testing should be conducted, especially for forensic purposes.

The identification of 6-MAM and/or heroin by mass spectrometry (MS)-based assays is accepted as a proof of previous heroin usage; however, morphine and its glucuronized metabolites are often the only opiates identified in the urine specimens after heroin usage due to the rapid removal of heroin and 6-MAM through metabolism. In this case, it is rather challenging to distinguish heroin usage from opium poppy (e.g., poppy seed) consumption by the laboratory findings. This creates a significant medicolegal issue known as "poppy seed defense" (Chen et al. 2014).

As discussed in the "Chemistry and Chemical Structures" section above, fentanyl and its analogues have a distinct structure to opiates (Figs. 1, 2 and 3); thus, any opiate immunoassays do not cross-react with these compounds (Liu et al. 2018). Instead, various immunoassays have been developed for fentanyl; however, most of them are for forensic or research use. Due to their strong structural similarity, these fentanyl assays should detect various fentanyl analogues with their high cross-reactivity. Currently there is only one FDA-cleared fentanyl immunoassay available on the market (SEFRIA™ Fentanyl Urine Enzyme Immunoassay, Immunalysis, Pomona, CA). The fentanyl immunoassay has not been incorporated in most standard drug screen immunoassay panels yet.

Similarly, any existing opiate immunoassays do not cross-react with U-47700, AH-7921, mitragynine, and 7-hydroxy mitragynine. Even though there are several immunoassay kits commercially available, these are for forensic or research use. There is no FDA-cleared immunoassay kit for these compounds.

Wide availability of FDA-cleared immunoassay kits should enable clinical laboratories to detect more cases of fentanyl (and/or fentanyl analogue) intoxication and misuse in a timely manner, potentially saving more lives.

Besides immunoassays, mass spectrometry (MS) – either gas chromatography-MS (GC-MS) or liquid chromatography-MS (LC-MS) – is used for identification of these synthetic opioids for clinical and forensic cases (summarized in Liu et al. 2018). These compounds can be detected by GC-MS-based untargeted analysis, but LC-MSMS-based targeted analysis is superior in the sensitivity of the assay (Liu et al. 2018).

2.6 Treatment

The primary danger associated with opioid toxicity is respiratory depression with hypercapnia, hypoxemia, and subsequent organ hypoperfusion injury, particularly of the brain and heart. The priority in treatment is to restore ventilation and oxygenation. Assisted ventilation through bag-valve-mask ventilation or endotracheal intubation treats the life-threatening respiratory toxicity associated with opioids. Naloxone, a μ-opioid receptor antagonist, is an effective antidote for acute opioid toxicity. Naloxone was approved for medical use in 1971. More recently, naloxone distribution for bystander use has resulted in reductions in opioid overdose mortality (McDonald and Strang 2016; Walley et al. 2013). Naloxone can be administered via intravenous, intramuscular, intranasal, and endotracheal routes. It is rapidly effective with reversal occurring within minutes of administration (Boyer 2012). Assisted ventilation should not be delayed while preparing or administering naloxone and should continue after administration until the patient is breathing independently. The adverse effects associated with naloxone administration are primarily related to induction of opioid withdrawal in opioid dependent patients (Wermeling 2015). Higher doses of naloxone may be needed depending upon the pharmacologic properties of different agents including receptor-binding affinity (Kd) and potency. However, when delivered promptly and effectively, naloxone is effective for reversal of even the most potent synthetic opioids and fentanyl analogues, though repeated escalating doses may be necessary in some cases (Armenian et al. 2018). If there is no response to even high-dose naloxone, intoxication with a non-opioid agent or advanced irreversible end-organ injury from prolonged hypoperfusion should be suspected. In some cases, the duration of action of the opioid will exceed that of naloxone. In such cases, repeated doses of naloxone and a naloxone infusion may be necessary to maintain ventilation throughout the course of toxicity, while the offending agent is metabolized and eliminated (Boyer 2012).

3 Cannabinoids

3.1 Epidemiology

Cannabis use dates back to ancient China in the fourth century BC and has been part of both social and medical culture since that time (Brand and Zhao 2017). In 1970, the US Controlled Substances Act classified marijuana as a Schedule I drug indicating a high risk of abuse without currently accepted medical use in the United States. However, cannabis-based medications have been approved by the FDA for human medical use including nabilone for chemotherapy-associated nausea and vomiting refractory to other agents; the Δ^9-tetrahydrocannabinol (THC) product, dronabinol, for appetite stimulation in anorexia associated with AIDS and nausea treatment for patients on chemotherapy; and, most recently, the cannabidiol (CBD) product, Epidiolex®, for treatment of specific seizure disorders. While cannabis remains Schedule I at the federal level in the United States, many states have passed legislation permitting the medical use of cannabis products with some states permitting recreational sale of cannabis. Legal status of cannabis is variable throughout the world. CBD, a constituent of marijuana without intoxicating properties, is not scheduled when sold in products that contain <0.3% THC, the primary psychoactive component of marijuana. Overall, marijuana use among Americans has risen significantly since 2003 with approximately 26 million marijuana users over the age of 12 in the United States in 2017 (Substance Abuse and Mental Health Services Administration (SAMHSA) 2018). Approximately 2.5% of the world's population consumes cannabis (World Health Organization Department of Mental Health and Substance Abuse Management of Substance Abuse Team (NMH/MSD/MSB) 2019). In 2008, the use of synthetic cannabinoids began to be recognized, first in Europe and then the United States (Auwarter et al. 2009; European Monitoring Centre for Drugs and Drug Addiction 2009). Their presence was identified in products sold as herbal incense products known colloquially as "K2" or "Spice," terms which have persisted and generally refer to myriad synthetic cannabinoid structures. At that time, the most commonly identified products were JWH-018, JWH-073, JWH-200, and CP-47,497 (Fig. 4) (Brents and Prather 2014). More recently, an even more potent class of synthetic cannabinoids has evolved with marked increases in reported exposures beginning in 2015 (Mowry et al. 2016). This group of cannabinoids including FUB-AMB, ADB-FUBINACA (Fig. 4), and many more are highly potent and result in much more significant toxicity (Table 1). The prevalence of synthetic cannabinoid use is unclear but growing (Law et al. 2015). Synthetic cannabinoids are the largest group of substances monitored by the EU Early Warning System, and cannabinoids were the most frequently seized novel psychoactive substances reported in 2016 (European Monitoring Centre for Drugs and Drug Addiction 2018). A significant barrier to more precise evaluation of prevalence is the difficulty in accurately identifying such a diverse group of continuously evolving chemicals in biological matrices (Castaneto et al. 2014). Synthetic cannabinoids can be identified in blood and urine specimens, but not in routine drug testing in typical healthcare settings highlighting the need for ongoing research and

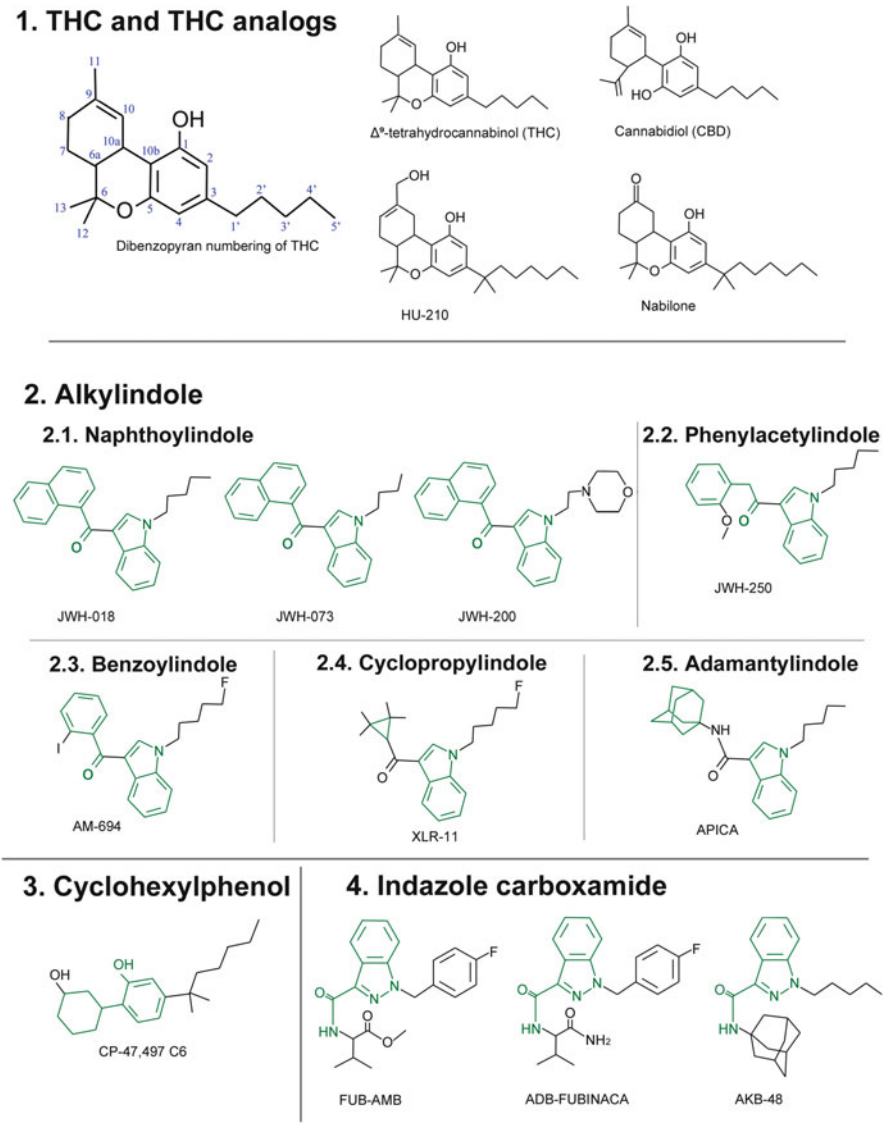

Fig. 4 Chemical structures of phytocannabinoids and synthetic cannabinoids. Based on the structure, these compounds are classified into four major groups: (1) Δ^9-tetrahydrocannabinol (THC) and THC analogues, (2) alkylindoles, (3) cyclohexylphenols, and (4) indazole carboxamide. The alkylindoles are further classified: (2.1) naphthoylindoles, (2.2) phenylacetylindoles, (2.3) benzoylindoles, (2.4) cyclopropylindoles, and (2.5) adamantylindoles. The core chemical structures in each synthetic cannabinoid are highlighted in green in the figure. The dibenzopyran numbering system of THC is also shown (Grotenhermen 2003; Mechoulam 1970)

attention to the application and interpretation of drug testing and surveillance for these compounds (Knittel et al. 2016).

3.2 Chemistry and Chemical Structures

THC is one of at least 113 phytocannabinoids identified in the *Cannabis* plant (Aizpurua-Olaizola et al. 2016). CBD is another phytocannabinoid identified in *Cannabis*. These cannabinoids are also synthesized in the laboratory. Other THC analogues are also synthesized; nabilone was developed by Eli Lilly (Lemberger and Rowe 1975), whereas HU-210 (11-OH-Δ8-THC-dimethylheptyl) was synthesized by Dr. Raphael Mechoulam at Hebrew University (HU) in Israel (Howlett et al. 1990; Mechoulam 2000). Based on the structural similarity, dibenzopyran numbering is widely applied to cannabinoids, even though cannabinoids do not contain any pyrans in their structure (Fig. 4) (Grotenhermen 2003; Mechoulam 1970).

Synthetic cannabinoids are classified into four major structural groups: (1) THC analogue, (2) alkylindole, (3) cyclohexylphenol, and (4) indazole carboxamide (Fig. 4) (Castaneto et al. 2014; Hill et al. 2018; Miliano et al. 2016; Smith et al. 2015; Wiley et al. 2015). Even though synthetic cannabinoids are potent CB1 (and CB2) cannabinoid receptor agonists, non-THC analogue compounds have the chemical structures distinct from that of THC.

The alkylindoles are further classified into several groups based on the structure (Miliano et al. 2016): naphthoylindoles (e.g., JWH-018, JWH-073, and JWH-200), phenylacetylindoles (e.g., JWH-250), benzoylindoles (e.g., AM-694), cyclopropylindoles (e.g., XLR-11), and adamantylindoles (e.g., APICA) (Fig. 4) (Hill et al. 2018; Miliano et al. 2016; Smith et al. 2015). The JWH-series of compounds was originally synthesized by Dr. John W. Huffman at Clemson University in South Carolina as part of his pharmacological research program of synthetic indole-derived cannabinoids (Wiley et al. 2015). The AM-series of compounds was originally developed by Dr. Alexandros Makriyannis at Northeastern University in Massachusetts. The cyclohexylphenols include CP-47.497 that was developed by Pfizer scientists (Weissman et al. 1982). The indazole carboxamides include FUB-AMB (also known as MMB-FUBINACA or AMB-FUBINACA), ADB-FUBINACA, and APINACA (AKB-48) (Gatch and Forster 2018; Hill et al. 2018). APINACA also contains an adamantayl group and has the indazole group in place of the indole ring in APICA, and thus it is structurally similar to APICA, an adamantylindole which can also be classified as an indole carboxamide (Fig. 4).

3.3 Pharmacology and Physiology Overview

Hundreds of cannabinoids, termed phytocannabinoids, and terpenoids have been identified in the *Cannabis* species of plants (Andre et al. 2016). The potential contribution of clinical effects from many of these constituents remains unclear. The primary focus of clinical and pharmacologic evaluation has been with the

cannabinoids, THC and CBD. The cannabinoid receptor system is complex with modulatory effects on multiple transmitter-receptor complexes and remains incompletely understood. Endogenous cannabinoids (endocannabinoids), anandamide and 2-arachidonoylglycerol, exert effects upon two identified cannabinoid receptors, CB1 and CB2 (Sugiura and Waku 2002). More recently, activity at the transient receptor potential vanilloid 1 (TRPV1) has been described with implications on both pain and hyperemesis syndromes (Zou and Kumar 2018). The CB1 receptor has been identified throughout the central and peripheral nervous systems with a wide variety of direct effects on neuronal, gastrointestinal, and immune cells as well as pre- and postsynaptic modulation of other neurotransmitters including GABA, acetylcholine, serotonin, glutamate, norepinephrine, and dopamine (Zou and Kumar 2018). Alternatively, CB2 receptors are primarily located in the spleen, testis, and with minimal role in the CNS reward system (Zou and Kumar 2018). Given the wide distribution of cannabinoid receptors and interaction with multiple neurologic pathways, activation results in a complex pattern of activity with many observed and hypothesized effects. THC is a partial agonist at the CB1 and CB2 receptors, while CBD has been described as an allosteric antagonist at cannabinoid receptors with serotonin and TRPV1 agonist activity (Boggs et al. 2018). The relative concentrations of THC and CBD in a cannabis product contribute to the variability in effect and experience with THC typically resulting in more psychoactivating intoxication, while CBD is responsible for the nonintoxicating effects described with cannabis use (Boggs et al. 2018). As opposed to the relatively weak cannabinoid receptor activation by endocannabinoids and the partial agonist and promiscuous activity of phytocannabinoids, synthetic cannabinoids have been developed as full cannabinoid receptor agonists resulting in much more potent activity by orders of magnitude depending upon the specific agent (Castaneto et al. 2014). Synthetic cannabinoids are often available as a liquid formulation which is then applied to vegetative material, e.g., marijuana or tobacco, or used in a vaporizing system. Onset of symptoms after inhalational use is rapid, typically within minutes, and duration can be hours to more than a day depending upon the dose and specific formulation (Castaneto et al. 2014). Marijuana metabolites can persist on urine drug screening for weeks depending upon frequency and magnitude of use (Lowe et al. 2009).

3.4 Clinical Effects

Given the diverse distribution and activity of cannabinoid receptors, there are a wide variety of proven, anecdotal, and theoretical therapeutic opportunities for pharmaceutical modulation. There is growing interest and support, both scientific and social, in the potential of cannabinoids for medical use, but high-level data are generally limited. As of 2017, there was strong evidence to support the benefits of cannabinoid use for nausea, appetite stimulation, modest reductions in chronic pain, and multiple sclerosis related spasticity. Otherwise, available research was unavailable or inadequate to draw definitive conclusions of benefit (National Academies of

Sciences and Medicine 2017). As further research is performed, additional supported indications for medical use may be validated. The diversity of cannabinoid effects also leads to a variety of intended and unintended consequences depending upon the formulation, route of delivery, and specific substance. For nonmedical use, intoxication and/or anxiolysis is typically the goal. Varying relative concentrations of THC and CBD in leaf marijuana as well as edibles, vaping oils, and other formulations of cannabinoids impact the nature and degree of intoxication with higher concentration of THC relative to CBD resulting in greater intoxication, motor impairment, and other adverse effects (Ford et al. 2017). There was a fourfold increase in THC content identified in confiscated marijuana in 2014 compared to 1995 with an increase in THC:CBD concentrations from 14 to 80 times (ElSohly et al. 2016). This rise in potency with availability of high concentration and pure THC alternative products as well as expanded availability has likely contributed to a rise in associated emergency department visits (Zhu and Wu 2016).

Acute phytocannabinoid toxicity is not life-threatening outside of associated trauma or secondary illness but can include impaired motor coordination, altered judgment, impaired short-term memory, nausea, vomiting, tachycardia, vasodilation with hypotension, syncope, paranoia, and psychosis (Volkow et al. 2014). Long-term adverse effects include addiction, impaired cognitive development with associated lower IQ (particularly in adolescent users), worsened educational outcomes, diminished life satisfaction and career achievement, chronic bronchitis, and increased risk of psychosis in individuals with an existing predisposition (Volkow et al. 2014). Cannabinoid hyperemesis syndrome has been described as a cyclical syndrome of vomiting, abdominal cramping, and dehydration in long-term regular users of cannabis with the hallmark feature of patients reporting relief from hot showers or baths (Sorensen et al. 2017).

Synthetic cannabinoids, as full cannabinoid receptor agonists, pose a much more significant immediate threat. In addition to symptoms associated with THC stimulation of cannabinoid receptors, synthetic cannabinoid use has been associated with extreme agitation, delirium, seizures, ventricular dysrhythmias, hemodynamic instability, respiratory failure, rhabdomyolysis, anoxic brain injury, and death (Katz et al. 2016). The degree of agitation and hyperadrenergic toxicity witnessed with use of these drugs is reminiscent of potent stimulant toxicity and may be clinically indistinguishable at the time of initial presentation. Given the relatively recent advent of synthetic cannabinoid availability, difficulty in identification, and limited experience with regular use, data regarding long-term effects are not available (Table 2).

3.5 Laboratory Detection and Methodology

FDA-cleared cannabinoid immunoassays are commonly included in routine urine drug screening panels. These kits are developed to target the inactive Δ9-THC carboxy metabolite, the major urinary excreted form, but they can cross-react with THC due to their structural similarity to the Δ9-THC carboxy metabolite. Some kits can even cross-react weakly with CBD at very high concentrations, as indicated in

the published data sheet (e.g., Syva® EMIT-II Plus Cannabinoid immunoassay kit, Siemens) and a published literature (Simpson et al. 1997). Furthermore, CBD products might contain a trace amount of THC (Bonn-Miller et al. 2017). Because of these facts, a urine specimen obtained from a CBD product user might generate a positive result of cannabinoid immunoassays either through its weak cross-reactivity with the immunoassay kit and/or the trace amount of THC included in the CBD products (Kulig 2017), especially if a large amount of CBD products is consumed and a low cutoff is adopted in the immunoassay.

Development of an immunoassay to detect synthetic cannabinoids in urine, the standard type of clinical specimens for analysis, is a challenging task. One major reason is their extensive metabolism. Another confounding factor is the wide structural diversity of these compounds (Fig. 4), which makes the development of a single immunoassay covering the whole class of synthetic cannabinoids unfeasible. Besides THC analogue HU-210, synthetic cannabinoids are structurally dissimilar to Δ9-THC or Δ9-THC carboxy metabolite, as predicted by 2D similarity values to Δ9-THC carboxy metabolite [e.g., JWH-018 (0.382), JWH-073 (0.345)]. That is why synthetic cannabinoids except THC analogues do not cross-react with THC immunoassays targeting Δ9-THC carboxy metabolite (Krasowski and Ekins 2014). Commercially available immunoassays for synthetic cannabinoids (e.g., Randox) can only cover relatively small groups of them with similar chemical structures (Arntson et al. 2013; Namera et al. 2015). None of these kits have received FDA clearance; thus, these kits cannot be used in clinical laboratories.

These limitations in immunoassays make LC-MSMS-based analysis the optimal alternative for the analysis of synthetic cannabinoids (Knittel et al. 2016; Namera et al. 2015; Scheidweiler and Huestis 2014). GC-MS seems not to be suitable for detection of synthetic cannabinoids without proper derivatization pretreatments, presumably because of their polar structures (Liu et al. 2018).

3.6 Treatment

The treatment of cannabinoid toxicity is largely supportive. There is no antidote for cannabinoid toxicity or clinically available CB1 receptor antagonist. Phytocannabinoid toxicity is self-limited, and treatment is aimed at symptom management with antiemetics, IV fluids, safe environment, redirection, and anxiolysis if necessary while intoxicated. Topical capsaicin has been recommended for the treatment of acute exacerbations of cannabinoid hyperemesis syndrome (Sorensen et al. 2017). The primary treatment for acute and chronic toxicity is cessation of use.

Management of synthetic cannabinoid toxicity is also supportive but typically requires much more intensive intervention including escalating doses of parenteral $GABA_A$-agonist medications including benzodiazepines and/or barbiturates to de-escalate agitated delirium associated with risk to both patients and care providers. In cases of severe agitation unresponsive to initial sedation and/or respiratory failure, endotracheal intubation may be necessary to provide adequate ventilation and sedative administration such as propofol or high-dose barbiturates, e.g.,

phenobarbital. Dosing should be titrated to sedation. Evaluation should include assessment of myocardial ischemia, infarction, or dysrhythmia with electrocardiogram and cardiac enzymes in patients with significant intoxication and cardiovascular vital sign abnormalities. Providers should have a low threshold to evaluate for rhabdomyolysis and associated kidney injury as well as aspiration pneumonitis/pneumonia which are common complications of both stimulant and sedative toxic syndromes. Patients with abnormal movements or encephalopathy out of proportion with intoxication or treatment should be evaluated for nonconvulsive seizure activity in addition to anoxic or traumatic brain injury (Castaneto et al. 2014; Katz et al. 2016).

4 Stimulants/Hallucinogens

4.1 Epidemiology

Cocaine and amphetamine/methamphetamine have been and remain the most commonly used illicit stimulants (Substance Abuse and Mental Health Services Administration (SAMHSA) 2018). Methamphetamine availability and purity are rising, while cost has remained low nationally resulting in increased prevalence of use (Drug Enforcement Administration (DEA) 2018a). Identification of cocaine and methamphetamine in postmortem evaluation of unintentional overdose death victims has risen steadily in recent years (Hedegaard et al. 2017). Additionally, prescription stimulants have been increasingly prescribed and misused (Safer 2016; Substance Abuse and Mental Health Services Administration (SAMHSA) 2018). A diverse group of novel stimulant and hallucinogenic drugs has also grown in popularity. The primary classes of newer stimulant psychoactive substances include β-ketoamphetamines (cathinones), piperazines, tryptamines, and two carbon (2C)-phenylethylamines (Fig. 5) (Graddy et al. 2018). Examples of these can be found in Table 1. Approximately 1.2% of surveyed adults self-reported use of psychoactive substances including cathinones and other novel phenylethylamines, while ~0.7% of high school students reported cathinone use from 2012 to 2014 (Palamar et al. 2015; Patrick et al. 2016). Cathinones are a group of stimulant chemicals derived from the *Catha edulis* (khat) plant. Chewing khat is a common cultural practice in many North African, Eastern Mediterranean, and Middle Eastern countries (Odenwald and al'Absi 2017). Western Europe and US utilization of synthetic stimulants derived from purified cathinone began to be reported in 2009–2010 at which time they were marketed as "bath salts," a name that has persisted and includes a wide variety of distinct cathinone derivatives and other stimulants (Prosser and Nelson 2012). These are often labelled, "Not for human consumption" in order to avoid regulation. While the DEA has classified many of these stimulants as Schedule I, continuous updates and changes to chemical structures make real-time accurate identification and

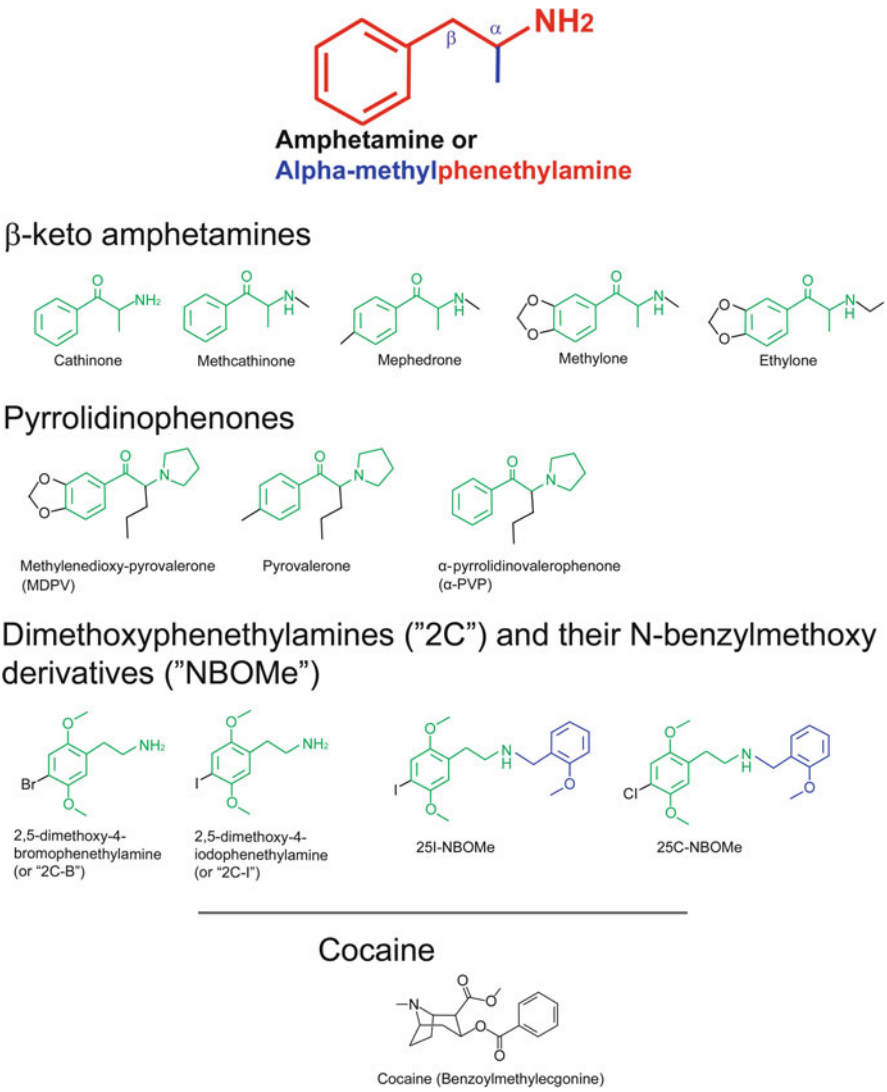

Fig. 5 Chemical structures of amphetamine, amphetamine-derived stimulants/hallucinogens, and cocaine. The chemical structure and nomenclature of amphetamine or alpha-methylphenethylamine are also provided in the figure. The core chemical structure of each class of amphetamine-type stimulants is highlighted in green and blue (for N-benzylmethoxy moiety)

response by regulating agencies difficult (Weinstein et al. 2017). The United Nations estimates that nearly 250 new drug analogues are created each year (Karch 2015). Forensic and clinical laboratories are challenged to keep pace with this fluid market of available stimulants (Glicksberg et al. 2016).

4.2 Chemistry and Chemical Structures

The prototypal compound is amphetamine, contracted from *alpha-m*ethyl-*phe*nethyl*amine*. Besides cocaine, these stimulants/hallucinogens are all amphetamine derivatives. These compounds are classified as β-keto amphetamines, pyrrolidinophenones, and dimethoxyphenethylamines (Fig. 5) (Peters and Martinez-Ramirez 2010; Petrie et al. 2013).

Cathinone is a prototypal β-keto amphetamine (Kalix 1992). There are numerous β-keto amphetamines or cathinone derivatives, including, but not limited to, methcathinone, mephedrone, methylone, and ethylone (Fig. 5).

Pyrrolidinophenones are another class of amphetamine-type stimulants which contain a pyrrolidine ring in place of the amine in the amphetamine skeleton. Examples of pyrrolidinophenones are α-pyrrolidinovalerophenone (α-PVP or "Flakka"), pyrovalerone, and methylenedioxy-pyrovalerone (MDPV) (Fig. 5).

Dimethoxyphenethylamines contain two methoxy groups attached to the 2- and 5-positions of the benzene ring in the phenethylamine backbone. These two carbon phenylethylamines are collectively called "2C." A bromine atom is attached to the 4-position of the benzene ring in 2,5-dimethoxy-4-bromophenethylamine or "2C-B," whereas an iodine atom is attached to the 4-position of the benzene ring in 2,5-dimethoxy-4-iodophenethylamine or "2C-I" (Fig. 5).

Dimethoxyphenethylamines have N-benzylmethoxy or *N-b*enzyl-*o*xy-*me*thyl derivatives called NBOMes. As the name indicates, a 2-methoxybenzyl group is attached to the nitrogen atom of the dimethoxyphenethylamines in NBOMes. The N-benzylmethoxy derivative of 2C-I or 25I-NBOMe [2-(4-Iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine] is the prototype of NBOMe (Fig. 5) (Laskowski et al. 2015).

Cocaine or benzoylmethylecgonine is a primary psychoactive tropane alkaloid in *Erythroxylum coca* leaves, structurally distinct from amphetamine-type stimulants/hallucinogens (Fig. 5) (Goldstein et al. 2009).

4.3 Pharmacology and Physiology Overview

Phenylethylamines stimulate the release and inhibit the reuptake of the biogenic amines norepinephrine, dopamine, and serotonin (Graddy et al. 2018). Structural variation imparts distinct patterns of neurotransmitter effects. For instance, methylenedioxymethamphetamine (MDMA) exerts greater serotonin effects leading to a more hallucinogenic experience compared to predominantly adrenergic symptoms with methamphetamine. The constellation of symptoms and clinical effects associated with individual drugs is dictated by the relative intensity of induced neurotransmitter activity. The "2C" compounds and their N-benzylmethoxy derivatives, e.g., 25I-NBOMe ("N-Bombs" or "Smiles"), are primarily potent serotonin receptor agonists with noradrenergic receptor activation, as well (Suzuki et al. 2015). Phenylethylamine drugs can be taken orally, smoked, or injected. 25I-NBOMe has also been sold on paper and referred to as "acid" which

can lead to confusion as that colloquial term has been used to describe lysergic diethylamide (LSD). Onset is typically rapid with duration of action of up to 8 h depending upon the specific product (Graddy et al. 2018).

Tryptamines, e.g., 5-Methoxy-N,N-diisopropyltryptamine (5-MeO-DiPT), also known as "Foxy" or "Foxy Methoxy," and piperazines, e.g., 1-benzylpiperazine (BZP) and 1-(3-Trifluoromethylphenyl)piperazine (TFMPP), have primarily serotonergic effects (Arbo et al. 2012; Dinis-Oliveira 2017; Dominguez-Clave et al. 2016).

4.4 Clinical Effects

Stimulants have been used clinically for a variety of purposes, particularly treatment of attention deficit hyperactivity disorder (ADHD) (Safer 2016). However, they also represent a broad and diverse group of illicitly available drugs from cocaine and methamphetamine to a variety of novel psychostimulants and hallucinogens. The toxicity associated with each drug and drug class is conferred by its neurotransmitter-receptor complex activity. Use of phenylethylamine compounds result in a mixture of noradrenergic, dopaminergic, and serotonergic effects including tachycardia, hypertension, diaphoresis, agitation, delirium, seizures, ventricular dysrhythmias, hallucinations, choreiform movements due to dopamine effects, tremor, hyperreflexia, and hyperthermia (Prosser and Nelson 2012). Tryptamines and piperazines, meanwhile, cause primarily serotonergic effects which overlap significantly but with more pronounced tremor and hyperreflexia and without evidence of dopamine-mediated effects such as chorea (Graddy et al. 2018). Dopamine and serotonin activity may both result in "hallucinations" though dopamine is more commonly associated with psychotic and tactile hallucinations, while serotonin is more likely to result in synesthesias (Rolland et al. 2014). Practically, differentiation of the various causative agents is difficult and unlikely to change immediate management. Hyponatremia has been reported with stimulant use, primarily with MDMA but also with the cathinone mephedrone (Prosser and Nelson 2012).

4.5 Laboratory Detection and Methodology

Currently there is no FDA-cleared immunoassay kit specifically targeting β-keto amphetamines, pyrrolidinophenones, and dimethoxyphenethylamine. Due to their moderate structural similarity to amphetamine (Fig. 5) [The 2D similarity value of cathinone, methcathinone, and mephedrone to amphetamine are all 0.45 (Petrie et al. 2013)], β-keto amphetamines appear to cross-react weakly with AxSYM® Amphetamine/Methamphetamine II, CEDIA Amphetamine/Ecstasy kit, and Lin-Zhi Methamphetamine enzyme immunoassays, but not EMIT® II Plus Amphetamines kit (Krasowski and Ekins 2014; Petrie et al. 2013; Regester et al. 2015).

Pyrrolidinophenones, on the other hand, appear not to cross-react with EMIT® II Plus Amphetamines kit, AxSYM® Amphetamine/Methamphetamine II, CEDIA Amphetamine/Ecstasy kit, and Lin-Zhi Methamphetamine enzyme immunoassay

due to weak structural similarity to amphetamine [The 2D similarity value of MDPV to amphetamine is 0.22 (Krasowski and Ekins 2014; Petrie et al. 2013; Regester et al. 2015)], but MDPV weakly cross-reacts with Microgenics DRI Phencyclidine enzyme assay, in accord with the moderate 2D similarity value of MDPV to PCP (0.52) (Krasowski and Ekins 2014; Macher and Penders 2013).

Dimethoxyphenethylamines ("2C" compounds) have rather weak structural similarity to amphetamine (Fig. 5) [The 2D similarity values of 2C-I and 2C-B to amphetamine are both 0.33 (Petrie 2013 Excel)]; 2Cs seem not to cross-react with AxSYM® Amphetamine/Methamphetamine II, CEDIA Amphetamine/Ecstasy kit, and Lin-Zhi Methamphetamine enzyme immunoassay; however they weakly cross-react with EMIT® II Plus Amphetamines kit (Petrie et al. 2013; Regester et al. 2015).

These amphetamine-derived stimulants/hallucinogens, at least β-keto amphetamines and pyrrolidinophenones, are detectable by GC-MS-based untargeted analysis without derivatization (Liu et al. 2018). Dimethoxyphenethylamines ("2C" compounds) including NBOMe are also detectable by GC-MS, even without derivatization (Ketha et al. 2017). These compounds are also detectable by LC-MS(MS) (Glicksberg et al. 2016; Laskowski et al. 2015; Namera et al. 2015).

4.6 Treatment

The mainstay of therapy for stimulant and hallucinogen toxicity is sedation to prevent harm associated with agitation. Early recognition and aggressive response to hyperthermia are critical as hyperthermia is an indicator of severe toxicity (Matsumoto et al. 2014). Treatment should include rapid titration of sedative agents including benzodiazepines and barbiturates to both control agitation as well as prevent potential seizures (Prosser and Nelson 2012). While tachycardia and hypertension are key findings, appropriate sedation will often improve both abnormalities. However, if sedation has been achieved, ancillary treatment of persistent severe tachycardia and/or hypertension with agents including α_1-adrenergic antagonists, α_2-adrenergic agonists, and calcium channel blockers is appropriate. Beta blockers are not recommended in the treatment of patients with acute sympathomimetic toxicity (Richards et al. 2017). Many patients will be volume depleted and require isotonic fluid resuscitation. Assessment of sodium concentration should be performed given the association of hyponatremia with some stimulants. Additionally, the psychomotor agitation often associated with stimulant and hallucinogen toxicity can lead to traumatic injuries and rhabdomyolysis with or without compartment syndrome. Careful examination of muscle compartments and for evidence of trauma is important in the management of agitated patients. While CT scan of the head is not absolutely indicated in all patients with agitated toxic encephalopathy, the threshold should be low given both the risks of trauma as well as the potential for intracranial hemorrhage associated with sudden extreme blood pressure elevation (Lappin et al. 2017). Likewise, cardiac evaluation for ischemia, infarction, and dysrhythmia should be performed. Cocaine, in particular, has sodium and potassium channel-blocking properties that can result in QRS and QT prolongation with ventricular

dysrhythmia that can be treated with sodium bicarbonate (Stankowski et al. 2015). In addition to GABA agonist sedation, which may require endotracheal intubation to achieve adequate sedation with airway protection, active cooling measures should be employed for hyperthermic patients. Adjunctive therapy with α_2-adrenergic agonists, e.g., dexmedetomidine, is appropriate for sedation as well as sympatholytic effects (Spiller et al. 2013). Patients with predominantly dopaminergic symptoms, including chorea or tactile hallucinations despite appropriate sedation, can be managed with parenteral antipsychotic agents (Wilson et al. 2012) (Table 2).

5 Dissociative Agents

5.1 Epidemiology

Arylcyclohexylamine derivatives of ketamine and phencyclidine have been used illicitly for decades with street names such as "Special K" and "Angel Dust," respectively. Dextromethorphan use, sometimes called "Robotripping" owing to its inclusion in Robitussin® cough suppressants, has also been common, particularly among adolescents (Morris and Wallach 2014). More recently, novel derivatives in this class have gained popularity including 3-methoxy-phencyclidine (3-MeO-PCP), methoxetamine, and 2-oxo-PCE (eticyclidone). Methoxetamine, in particular, emerged through online sales beginning in 2010 (Corazza et al. 2013).

5.2 Chemistry and Chemical Structures

Arylcyclohexylamine derivatives have a phenylcyclohexylamine skeleton (Fig. 6). Phencyclidine or PCP (contracted from "1-(1-*P*henyl*c*yclohexyl)piperidine") is the prototypal compound in this class (Dove 1984). PCP was synthesized as a general anesthetic by Victor Maddox at Parke-Davis in 1956. Even though PCP was quickly abandoned in the clinical scene because of adverse effects in 1963, various arylcyclohexylamine derivatives have been developed at Parke-Davis. A methoxy group is added to the 3-position of the aromatic ring of PCP in 3-MeO-PCP (3-methoxyl-phencyclidine). The piperidine ring of PCP is substituted with the methylamino group in ketamine. Similarly, the piperidine ring of PCP is substituted with the ethylamino group in N-*e*thyl-1-*p*henyl*c*yclohexylamine (PCE) or eticyclidine. An oxo (or "=O") group is attached to the 2-position of the cyclohexyl ring of PCE in eticyclidone or 2-oxo-PCE. A methoxy group is added to the 3-position of the aromatic ring of PCE in 3-methoxyl-eticyclidine (3-MeO-PCE). A methoxy group is further attached to the 3-position of the aromatic ring of eticyclidone in methoxetamine (MXE) (Morris and Wallach 2014).

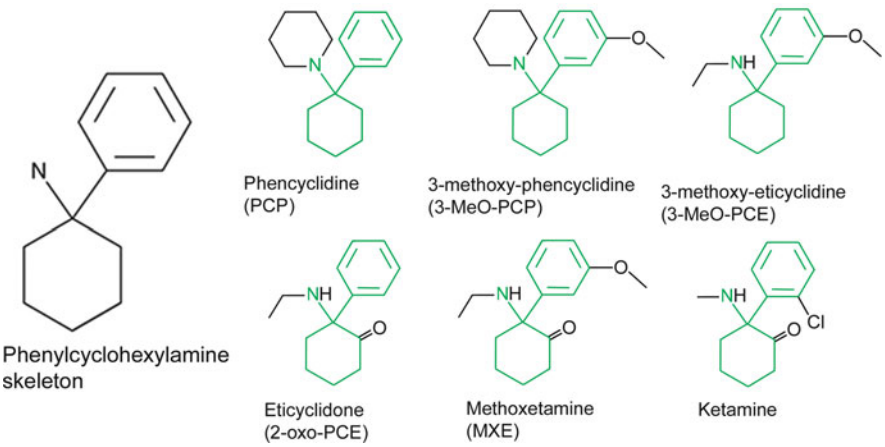

Fig. 6 Chemical structures of arylcyclohexylamines. The phenylcyclohexylamine skeleton is also provided in the figure. The core phenylcyclohexylamine skeleton is also highlighted in each compound in green

5.3 Pharmacology and Physiology Overview

Dissociative agents typically exert their primary pharmacologic effect through blockade of excitatory N-methyl-d-aspartate (NMDA) receptors (Lodge and Mercier 2015). NMDA receptors are stimulated by glutamate and glycine with resulting influx of cations including calcium and sodium (Lakhan et al. 2013). Additional activity as a relatively weak opioid and dopamine receptor agonist has been described as well as effects on serotonergic and noradrenergic pathways (Peltoniemi et al. 2016). The duration of action of phencyclidine and ketamine is relatively brief with a half-life of 2–4 h (Sinner and Graf 2008). However, ketamine and phencyclidine derivative novel psychoactive substances are reported to have longer duration of action than the parent compounds (Corazza et al. 2012). Novel ketamine and phencyclidine derivatives and analogues would be anticipated to share mechanistic function due to class effect, particularly given the reported similarity in clinical syndromes, but dedicated pharmacologic and pharmacokinetic investigation of newly emerging drugs cannot maintain pace with discovery.

5.4 Clinical Effects

Antagonists of the NMDA receptor are promising in the management of a number of acute and chronic conditions. Dissociative agents have been used increasingly for the management of pain, seizures, anesthesia, and alcohol withdrawal (Peltoniemi et al. 2016; Pizon et al. 2018). More recently, there is a growing body of evidence suggesting benefits in the treatment of depression with ketamine and its enantiomer,

s-ketamine (Molero et al. 2018). Dextromethorphan, while technically an opioid, is used primarily for its NMDA antagonizing activity (Morris and Wallach 2014). Dissociative symptoms serve as the basis for both desired as well as unintended effects in clinical and recreational use. Despite the common media narrative of severe agitation and superhuman strength associated with use of phencyclidine, the reality is typically much less severe. Clinical effects include a dissociation of thought from the body which can contribute to psychotomimetic effects and the potential for agitation with a detachment of central perception from peripheral pain and action (Morris and Wallach 2014). Additionally, tachycardia, hypertension, catatonia, and nystagmus are hallmark features. A spiritual or "near death" experience is also frequently reported (Corazza et al. 2013).

5.5 Laboratory Detection and Methodology

PCP immunoassays are included as part of routine urine drug screening panels. PCP immunoassays should cross-react with 3-MeO-PCP due to its structural similarity; indeed, the EMIT-II Plus PCP immunoassay exhibits 100% cross-reactivity with 3-Me-PCP (Skaugen et al. 2019). Other arylcyclohexylamine derivatives such as 2-oxo-PCE are not expected to cross-react with PCP immunoassay kits due to the limited structural similarity unless the concentrations of these compounds are very high in the specimen. PCP immunoassays are also known to cross-react various drugs of other classes, such as dextromethorphan, venlafaxine, or tramadol, due to remote structural similarity to PCP (King et al. 2013; Krasowski et al. 2009; Sena et al. 2002).

5.6 Treatment

Toxicity associated with arylcyclohexylamines and related NMDA receptor antagonists is primarily related to the potential for agitation as well as injury associated with dissociative intoxication. Significant cardiovascular toxicity from tachycardia and hypertension as well as seizures have also been reported with the use of newer, more potent analogues (Morris and Wallach 2014). Initial treatment includes providing a safe environment, redirection and reassurance if the patient is demonstrating dysphoric effects, and observation with hydration. However, patients displaying agitation posing a threat to themselves or others should be treated with escalating doses of $GABA_A$ agonists, primarily benzodiazepines (Helander et al. 2015) (Table 2).

6 Sedative-Hypnotics

6.1 Epidemiology

Sedative-hypnotic use and misuse have historically involved prescription pharmaceuticals, e.g., alprazolam, lorazepam, and clonazepam. As opioids have become more tightly regulated and prescribing has declined, prescription alternatives for pain and muscle relaxation have been increasingly utilized with associated rises in misuse and toxicity. Gabapentin and baclofen are commonly used as non-opioid analgesics for neuropathic and musculoskeletal pain. Since 2012, toxicity associated with recreational use of each has accelerated (Shulman et al. 2017). Gabapentin misuse has been estimated as affecting 1% of the population, particularly affecting patients who have an associated opioid use disorder (Smith et al. 2016). At the same time, designer benzodiazepines unavailable for legal prescription or sale in the United States including etizolam and clonazolam, among others, have become increasingly available (Carpenter et al. 2018). Other emerging sedative-hypnotics include phenibut, which is available on the Internet. Phenibut overdose cases have been observed sporadically (Downes et al. 2015; Wong et al. 2015).

6.2 Chemistry and Chemical Structures

γ-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the brain. Most sedative-hypnotics are GABA receptor agonists and/or GABA derivatives. Baclofen, gabapentin, and phenibut (β-phenyl-γ-butyric acid) are all GABA derivatives (Fig. 7). Baclofen was first developed in 1962 by Heinrich Keberle of Ciba in Basel, Switzerland, by adding an aromatic ring to the GABA molecule to increase penetration of the blood-brain barrier (Lapin 2001; Yogeeswari et al. 2006). Similarly, phenibut was developed by Perekalin in Russia in 1964 (Lapin 2001). Gabapentin was developed by adding a cyclohexane ring to GABA molecule at Parke-Davis in 1974 (Satzinger et al. 1975).

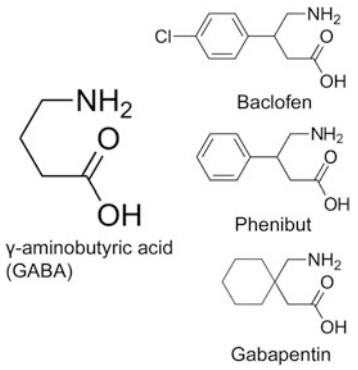

Fig. 7 Chemical structures of γ-aminobutyric acid (GABA) and its derivatives: baclofen, phenibut (β-phenyl-γ-butyric acid), and gabapentin

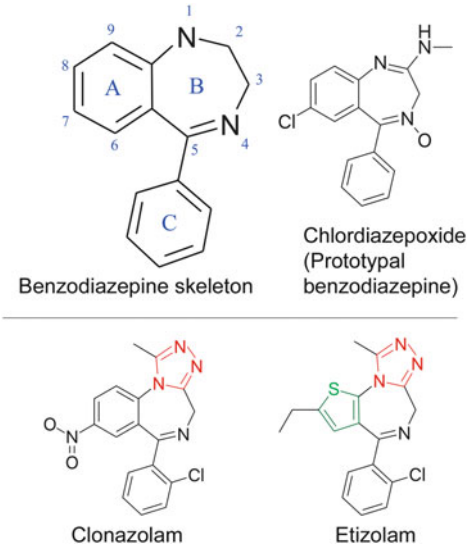

Fig. 8 Chemical structures of benzodiazepines and thienodiazepine. The benzodiazepine skeleton is comprised of the benzene ring (A) fused to a 1,4-diazepine ring (B) and an aryl group (ring C) attached to the 5-position of the diazepine ring (B). A triazole ring (highlighted in red) is fused to the diazepine ring (B) in clonazolam. A thiophene (highlighted in green) substitutes the benzene ring (A), and a triazole ring (highlighted in red) is fused to the diazepine ring (B) in etizolam, one of the thienotriazolodiazepines. The chemical structure of the prototypal benzodiazepine chlordiazepoxide is also shown as a reference in the figure

The prototypal benzodiazepine chlordiazepoxide was first developed in 1960 by Leo Sternbach at Hoffmann-La Roche as a novel synthetic tranquilizer (Sternbach 1979). As the name implies, the benzodiazepine skeleton has a characteristic ring structure with the benzene ring (A) fused to a 1,4-diazepine ring (B). In addition, an aryl group (ring C) is attached to the 5-position of the diazepine ring (B) (Childress and Gluckman 1964) (Fig. 8). Various modifications have been made to develop numerous benzodiazepines. Clonazolam has a triazole ring fused to the 1,4-diazepine ring (B) of the benzodiazepine skeleton. Etizolam also contains a triazole ring fused to the 1,4-diazepine ring (B); however, the diazepine ring is fused to thiophene, not to the benzene ring. That is why it is classified as thienotriazolodiazepine, not benzodiazepine (Tahara et al. 1978).

6.3 Pharmacology and Physiology Overview

Benzodiazepines and other sedative-hypnotics typically act on GABA receptors. From a clinical perspective, the primary GABA receptor subtypes are $GABA_A$ ionotropic and $GABA_B$ metabotropic inhibitory receptors. Each type leads to hyperpolarization, thus causing decreased cellular activity (Jembrek and Vlainic 2015). $GABA_A$ receptor ligands include prescription and designer benzodiazepines,

thienotriazolodiazepines, and other sedatives. Both benzodiazepines and thienotriazolodiazepines bind to an allosteric site on the $GABA_A$ receptor; thus, their action depends upon endogenously available GABA (Sanger 2004; Sieghart 2015). $GABA_B$ receptor ligands include baclofen and phenibut among others. $GABA_B$ receptors are distributed on both pre- and postsynaptic membranes and play roles in glutamate release and feedback inhibition of GABA release leading to a heterogeneity of clinical response. Gabapentin is structurally analogous to GABA but does not appear to affect GABA receptors rather inducing sedative effects through the inhibition of voltage-gated calcium channels resulting in reduced excitatory neurotransmitter release (Bockbrader et al. 2010).

6.4 Clinical Effects

As the class name implies, the primary associated clinical effect of sedative use is relaxation, anxiolysis, and sedation, particularly with $GABA_A$ agonists. Typically, individuals suffering $GABA_A$-agonist toxicity will be sedate with relatively minimal effect on heart rate and blood pressure. Airway protective reflexes can be diminished, and reduction in respiratory drive may be observed, especially with concurrent use of another sedative or opioid (Horsfall and Sprague 2017). $GABA_B$-agonist toxicity can be much more diverse. Given the presynaptic distribution of $GABA_B$ receptors with associated inhibition of GABA neurotransmitter release in addition to glutamatergic modulation, $GABA_B$ receptor agonist toxicity may result in sedation, agitation, or an alternating syndrome with both mental states. Additionally, sinus tachycardia, hyperreflexia, and myoclonic jerks may be present unlike with $GABA_A$ toxicity (Schep et al. 2012).

6.5 Laboratory Detection and Methodology

Benzodiazepine immunoassays are included as part of routine urine drug screening panels. Clonazolam and etizolam are moderately detectable by some benzodiazepine immunoassay kits (e.g., CEDIA Benzodiazepine Assay), but these compounds are less detected by other kits (e.g., Syva® EMIT-II Plus Benzodiazepine Assay) (Pettersson Bergstrand et al. 2017; van Wijk et al. 2018). The immunoassays cannot discern designer benzodiazepines/thienodiazepines from prescribed ones because the immunoassays are only capable of screening the presence of multiple compounds within the same class. MS-based assays are required for the identification and confirmation of these compounds, specifically. Indeed, these compounds are successfully identified in serum and urine by LC-high resolution MS (van Wijk et al. 2018).

Regarding the GABA derivatives (baclofen, gabapentin, and phenibut), there are no immunoassays for these compounds commercially available. These compounds are, however, detectable by either GC-MS (Lee et al. 2017; Van Lente and Gatautis 1998) or LC-MS (MS) (Downes et al. 2015; Grinberga et al. 2008; Hou et al. 2014).

Several reference laboratories offer LC-MS(MS)-based quantitative assays for gabapentin and baclofen, but no reference laboratories offer a phenibut assay in the United States (Table 2).

6.6 Treatment

The management of GABA-mediated toxicity is primarily supportive with endotracheal intubation and ventilator therapy for patients who are either unable to protect their airways or who demonstrate evidence of respiratory failure. Flumazenil, a benzodiazepine-specific antagonist on the $GABA_A$ receptor, can be considered in the management of acute sedative-hypnotic toxicity for both therapeutic and diagnostic purposes. Its use is primarily recommended in pediatric populations, patients with isolated benzodiazepine toxicity without known dependence, or those in whom iatrogenic benzodiazepine sedation has resulted in significant adverse effects in order to avoid respiratory complications. However, given the relatively low but real risk of serious adverse events including cardiac dysrhythmias, seizures, agitation associated with abrupt induction of precipitated withdrawal, and/or unmasking of co-occurring stimulant toxicity in contrast to the relatively low risk of toxicity in a medically supervised setting, routine use of flumazenil is not recommended (Penninga et al. 2016).

7 Conclusion

Nonmedical use of medications and illicit drugs represents a critical public health threat worldwide. In the United States, the life expectancy of Americans in 2018 declined due to unintentional overdose and suicide. Overdose deaths have risen substantially in a relatively short period of time and continue to rise each year. In addition to the incredible toll substance use has had on mortality, the overall effect across society is even greater. The nature and prevalence of drugs have evolved over time with a recent acceleration in the variety of chemicals available for use in conjunction with increased ease of access. The result is an incredibly diverse group of novel psychoactive substances derived from traditional categories of drugs which pose significant challenges to healthcare, public health, regulatory, and law enforcement systems. Coordination of these systems built upon accurate identification and surveillance of the rapidly changing environment of drug use is necessary to inform effective and timely therapeutic and policy response to this public health crisis. FDA-cleared immunoassay kits covering these emerging drugs of abuse are required for rapid detection of these drugs in the clinic and hospital (Table 2).

Acknowledgments We are thankful to Jacqueline A. Rymer and Spiros Giannoutsos for their technical assistance in the laboratory.

References

Aizpurua-Olaizola O, Soydaner U, Ozturk E, Schibano D, Simsir Y, Navarro P, Etxebarria N, Usobiaga A (2016) Evolution of the cannabinoid and terpene content during the growth of cannabis sativa plants from different chemotypes. J Nat Prod 79:324–331. https://doi.org/10.1021/acs.jnatprod.5b00949

Andre CM, Hausman JF, Guerriero G (2016) Cannabis sativa: the plant of the thousand and one molecules. Front Plant Sci 7:19. https://doi.org/10.3389/fpls.2016.00019

Arbo MD, Bastos ML, Carmo HF (2012) Piperazine compounds as drugs of abuse. Drug Alcohol Depend 122:174–185. https://doi.org/10.1016/j.drugalcdep.2011.10.007

Armenian P, Vo KT, Barr-Walker J, Lynch KL (2018) Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review. Neuropharmacology 134:121–132. https://doi.org/10.1016/j.neuropharm.2017.10.016

Arntson A, Ofsa B, Lancaster D, Simon JR, McMullin M, Logan B (2013) Validation of a novel immunoassay for the detection of synthetic cannabinoids and metabolites in urine specimens. J Anal Toxicol 37:284–290. https://doi.org/10.1093/jat/bkt024

Auwarter V, Dresen S, Weinmann W, Muller M, Putz M, Ferreiros N (2009) 'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? J Mass Spectrom 44:832–837. https://doi.org/10.1002/jms.1558

Baldo BA (2018) Opioid analgesic drugs and serotonin toxicity (syndrome): mechanisms, animal models, and links to clinical effects. Arch Toxicol 92:2457–2473. https://doi.org/10.1007/s00204-018-2244-6

Behzadi M, Joukar S, Beik A (2018) Opioids and cardiac arrhythmia: a literature review. Med Princ Pract 27:401–414. https://doi.org/10.1159/000492616

Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P (2010) A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet 49:661–669. https://doi.org/10.2165/11536200-000000000-00000

Boggs DL, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M (2018) Clinical and preclinical evidence for functional interactions of cannabidiol and delta(9)-tetrahydrocannabinol. Neuropsychopharmacology 43:142–154. https://doi.org/10.1038/npp.2017.209

Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R (2017) Labeling accuracy of cannabidiol extracts sold online. JAMA 318:1708–1709. https://doi.org/10.1001/jama.2017.11909

Boom M, Niesters M, Sarton E, Aarts L, Smith TW, Dahan A (2012) Non-analgesic effects of opioids: opioid-induced respiratory depression. Curr Pharm Des 18:5994–6004

Boyer EW (2012) Management of opioid analgesic overdose. N Engl J Med 367:146–155. https://doi.org/10.1056/NEJMra1202561

Brand EJ, Zhao Z (2017) Cannabis in chinese medicine: are some traditional indications referenced in ancient literature related to cannabinoids? Front Pharmacol 8:108. https://doi.org/10.3389/fphar.2017.00108

Brents LK, Prather PL (2014) The K2/spice phenomenon: emergence, identification, legislation and metabolic characterization of synthetic cannabinoids in herbal incense products. Drug Metab Rev 46:72–85. https://doi.org/10.3109/03602532.2013.839700

Brittain RT, Kellett DN, Neat ML, Stables R (1973) Proceedings: anti-nociceptive effects in N-substituted cyclohexylmethylbenzamides. Br J Pharmacol 49:158P–159P

Broseus J, Gentile N, Esseiva P (2016) The cutting of cocaine and heroin: a critical review. Forensic Sci Int 262:73–83. https://doi.org/10.1016/j.forsciint.2016.02.033

Carpenter JE, Murray BP, Dunkley C, Kazzi ZN, Gittinger MH (2018) Designer benzodiazepines: a report of exposures recorded in the National Poison Data System, 2014–2017. Clin Toxicol (Phila) 57(4):282–286. https://doi.org/10.1080/15563650.2018.1510502

Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA (2014) Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend 144:12–41. https://doi.org/10.1016/j.drugalcdep.2014.08.005

Cayman Chemical Standardized Naming of Substituted Fentanyls. https://www.caymanchem.com/Literature/standardized-naming-of-substituted-fentanyls. Accessed 4 Dec 2018

Chen P, Braithwaite RA, George C, Hylands PJ, Parkin MC, Smith NW, Kicman AT (2014) The poppy seed defense: a novel solution. Drug Test Anal 6:194–201. https://doi.org/10.1002/dta.1590

Childress SJ, Gluckman MI (1964) 1,4-Benzodiazepines. J Pharm Sci 53:577–590

Corazza O, Schifano F, Simonato P, Fergus S, Assi S, Stair J, Corkery J, Trincas G, Deluca P, Davey Z, Blaszko U, Demetrovics Z, Moskalewicz J, Enea A, di Melchiorre G, Mervo B, di Furia L, Farre M, Flesland L, Pasinetti M, Pezzolesi C, Pisarska A, Shapiro H, Siemann H, Skutle A, Enea A, di Melchiorre G, Sferrazza E, Torrens M, van der Kreeft P, Zummo D, Scherbaum N (2012) Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine. Hum Psychopharmacol 27:145–149. https://doi.org/10.1002/hup.1242

Corazza O, Assi S, Schifano F (2013) From "Special K" to "Special M": the evolution of the recreational use of ketamine and methoxetamine. CNS Neurosci Ther 19:454–460. https://doi.org/10.1111/cns.12063

Daniulaityte R, Juhascik MP, Strayer KE, Sizemore IE, Harshbarger KE, Antonides HM, Carlson RR (2017) Overdose deaths related to fentanyl and its analogs – Ohio, January-February 2017. MMWR Morb Mortal Wkly Rep 66:904–908. https://doi.org/10.15585/mmwr.mm6634a3

Devereaux AL, Mercer SL, Cunningham CW (2018) DARK classics in chemical neuroscience: morphine. ACS Chem Neurosci 9:2395–2407. https://doi.org/10.1021/acschemneuro.8b00150

Dinis-Oliveira RJ (2017) Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance. Drug Metab Rev 49:84–91. https://doi.org/10.1080/03602532.2016.1278228

Dominguez-Clave E, Soler J, Elices M, Pascual JC, Alvarez E, de la Fuente RM, Friedlander P, Feilding A, Riba J (2016) Ayahuasca: pharmacology, neuroscience and therapeutic potential. Brain Res Bull 126:89–101. https://doi.org/10.1016/j.brainresbull.2016.03.002

Domino EF (2008) Dr. Paul: views through the piperidine ring. Anesth Analg 107:723–724; author reply 724. https://doi.org/10.1213/ane.0b013e31817c737d

Dove HW (1984) Phencyclidine: pharmacologic and clinical review. Psychiatr Med 2:189–209

Downes MA, Berling IL, Mostafa A, Grice J, Roberts MS, Isbister GK (2015) Acute behavioural disturbance associated with phenibut purchased via an internet supplier. Clin Toxicol (Phila) 53:636–638. https://doi.org/10.3109/15563650.2015.1059945

Drug Enforcement Administration (DEA) (2017) 2017 National drug threat assessment. In: U.S. Department of Justice (ed)

Drug Enforcement Administration (DEA) (2018a) 2018 National drug threat assessment. In: U.S. Department of Justice (ed)

Drug Enforcement Administration (DEA) (2018b) Emerging threat report, annual 2017. In: U.S. Department of Justice (ed)

Drug Enforcement Administration (DEA) (2018c) Emerging threat report, mid-year 2018. In: U.S. Department of Justice (ed)

ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC (2016) Changes in cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States. Biol Psychiatry 79:613–619. https://doi.org/10.1016/j.biopsych.2016.01.004

European Monitoring Centre for Drugs and Drug Addiction (2009) Understanding the 'Spice' phenomenon. Publications Office of the European Union, Luxembourg

European Monitoring Centre for Drugs and Drug Addiction (2018) Fentanils and synthetic cannabinoids: driving greater complexity into the drug situation. An update from the EU Early Warning System. Publications Office of the European Union, Luxembourg

Florence CS, Zhou C, Luo F, Xu L (2016) The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care 54:901–906. https://doi.org/10.1097/MLR.0000000000000625

Ford TC, Hayley AC, Downey LA, Parrott AC (2017) Cannabis: an overview of its adverse acute and chronic effects and its implications. Curr Drug Abuse Rev 10:6–18. https://doi.org/10.2174/1874473710666170712113042

Gatch MB, Forster MJ (2018) Cannabinoid-like effects of five novel carboxamide synthetic cannabinoids. Neurotoxicology 70:72–79. https://doi.org/10.1016/j.neuro.2018.11.004

Gendron L, Cahill CM, von Zastrow M, Schiller PW, Pineyro G (2016) Molecular pharmacology of delta-opioid receptors. Pharmacol Rev 68:631–700. https://doi.org/10.1124/pr.114.008979

Genzen JR, Mohlman JS, Lynch JL, Squires MW, Weiss RL (2017) Laboratory-developed tests: a legislative and regulatory review. Clin Chem 63:1575–1584. https://doi.org/10.1373/clinchem.2017.275164

Glicksberg L, Bryand K, Kerrigan S (2016) Identification and quantification of synthetic cathinones in blood and urine using liquid chromatography-quadrupole/time of flight (LC-Q/TOF) mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 1035:91–103. https://doi.org/10.1016/j.jchromb.2016.09.027

Goldberger BA, Darwin WD, Grant TM, Allen AC, Caplan YH, Cone EJ (1993) Measurement of heroin and its metabolites by isotope-dilution electron-impact mass spectrometry. Clin Chem 39:670–675

Goldstein RA, DesLauriers C, Burda AM (2009) Cocaine: history, social implications, and toxicity--a review. Dis Mon 55:6–38. https://doi.org/10.1016/j.disamonth.2008.10.002

Graddy R, Buresh ME, Rastegar DA (2018) New and emerging illicit psychoactive substances. Med Clin North Am 102:697–714. https://doi.org/10.1016/j.mcna.2018.02.010

Grinberga S, Zvejniece L, Liepinsh E, Dambrova M, Pugovics O (2008) Quantitative analysis of phenibut in rat brain tissue extracts by liquid chromatography-tandem mass spectrometry. Biomed Chromatogr 22:1321–1324. https://doi.org/10.1002/bmc.1059

Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 42:327–360. https://doi.org/10.2165/00003088-200342040-00003

Guy GP Jr, Zhang K, Bohm MK, Losby J, Lewis B, Young R, Murphy LB, Dowell D (2017) Vital signs: changes in opioid prescribing in the United States, 2006-2015. MMWR Morb Mortal Wkly Rep 66:697–704. https://doi.org/10.15585/mmwr.mm6626a4

Hassamal S, Miotto K, Dale W, Danovitch I (2018) Tramadol: understanding the risk of serotonin syndrome and seizures. Am J Med 131:1382.e1–1382.e6. https://doi.org/10.1016/j.amjmed.2018.04.025

Hedegaard H, Warner M, Minino AM (2017) Drug overdose deaths in the United States, 1999-2016. NCHS Data Brief 294:1–8

Helander A, Beck O, Backberg M (2015) Intoxications by the dissociative new psychoactive substances diphenidine and methoxphenidine. Clin Toxicol (Phila) 53:446–453. https://doi.org/10.3109/15563650.2015.1033630

Hill SL, Dunn M, Cano C, Harnor SJ, Hardcastle IR, Grundlingh J, Dargan PI, Wood DM, Tucker S, Bartram T, Thomas SHL (2018) Human toxicity caused by indole and indazole carboxylate synthetic cannabinoid receptor agonists: from horizon scanning to notification. Clin Chem 64:346–354. https://doi.org/10.1373/clinchem.2017.275867

Horsfall JT, Sprague JE (2017) The pharmacology and toxicology of the 'Holy Trinity'. Basic Clin Pharmacol Toxicol 120:115–119. https://doi.org/10.1111/bcpt.12655

Hou XL, Wu YL, Chen RX, Zhu Y, Lv Y, Xu XQ (2014) Evaluation of two modified quick, easy, cheap, effective, rugged and safe (QuEChERS) sample preparation methods for the analysis of baclofen and gabapentin in feeds by liquid chromatography tandem mass spectrometry. J Pharm Biomed Anal 88:53–59. https://doi.org/10.1016/j.jpba.2013.08.026

Howlett AC, Champion TM, Wilken GH, Mechoulam R (1990) Stereochemical effects of 11-OH-delta 8-tetrahydrocannabinol-dimethylheptyl to inhibit adenylate cyclase and bind to the cannabinoid receptor. Neuropharmacology 29:161–165

Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS (2018) Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. Science 361:eaau1184. https://doi.org/10.1126/science.aau1184

Jansen KL, Prast CJ (1988) Ethnopharmacology of kratom and the Mitragyna alkaloids. J Ethnopharmacol 23:115–119

Jembrek MJ, Vlainic J (2015) GABA receptors: pharmacological potential and pitfalls. Curr Pharm Des 21:4943–4959

Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT (2018) A brief history of the opioid epidemic and strategies for pain medicine. Pain Ther 7:13–21. https://doi.org/10.1007/s40122-018-0097-6

Kalix P (1992) Cathinone, a natural amphetamine. Pharmacol Toxicol 70:77–86

Karch SB (2015) Cathinone neurotoxicity ("The 3Ms"). Curr Neuropharmacol 13:21–25. https://doi.org/10.2174/1570159X13666141210225009

Katz KD, Leonetti AL, Bailey BC, Surmaitis RM, Eustice ER, Kacinko S, Wheatley SM (2016) Case series of synthetic cannabinoid intoxication from one toxicology center. West J Emerg Med 17:290–294. https://doi.org/10.5811/westjem.2016.2.29519

Ketha H, Webb M, Clayton L, Li S (2017) Gas chromatography mass spectrometry (GC-MS) for identification of designer stimulants including 2C amines, NBOMe compounds, and cathinones in urine. Curr Protoc Toxicol 74:4.43.1–4.43.10. https://doi.org/10.1002/cptx.33

King AM, Pugh JL, Menke NB, Krasowski MD, Lynch MJ, Pizon AF (2013) Nonfatal tramadol overdose may cause false-positive phencyclidine on Emit-II assay. Am J Emerg Med 31(444): e5–e9. https://doi.org/10.1016/j.ajem.2012.05.028

Knittel JL, Holler JM, Chmiel JD, Vorce SP, Magluilo J Jr, Levine B, Ramos G, Bosy TZ (2016) Analysis of parent synthetic cannabinoids in blood and urinary metabolites by liquid chromatography tandem mass spectrometry. J Anal Toxicol 40:173–186. https://doi.org/10.1093/jat/bkv137

Krasowski MD, Ekins S (2014) Using cheminformatics to predict cross reactivity of "designer drugs" to their currently available immunoassays. J Cheminform 6:22. https://doi.org/10.1186/1758-2946-6-22

Krasowski MD, Pizon AF, Siam MG, Giannoutsos S, Iyer M, Ekins S (2009) Using molecular similarity to highlight the challenges of routine immunoassay-based drug of abuse/toxicology screening in emergency medicine. BMC Emerg Med 9:5. https://doi.org/10.1186/1471-227X-9-5

Kreek MJ, Levran O, Reed B, Schlussman SD, Zhou Y, Butelman ER (2012) Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. J Clin Invest 122:3387–3393. https://doi.org/10.1172/JCI60390

Kruegel AC, Grundmann O (2018) The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology 134:108–120. https://doi.org/10.1016/j.neuropharm.2017.08.026

Kulig K (2017) Interpretation of workplace tests for cannabinoids. J Med Toxicol 13:106–110. https://doi.org/10.1007/s13181-016-0587-z

Lakhan SE, Caro M, Hadzimichalis N (2013) NMDA receptor activity in neuropsychiatric disorders. Front Psychiatry 4:52. https://doi.org/10.3389/fpsyt.2013.00052

Lapin I (2001) Phenibut (beta-phenyl-GABA): a tranquilizer and nootropic drug. CNS Drug Rev 7:471–481

Lappin JM, Darke S, Farrell M (2017) Stroke and methamphetamine use in young adults: a review. J Neurol Neurosurg Psychiatry 88:1079–1091. https://doi.org/10.1136/jnnp-2017-316071

Laskowski LK, Elbakoush F, Calvo J, Exantus-Bernard G, Fong J, Poklis JL, Poklis A, Nelson LS (2015) Evolution of the NBOMes: 25C- and 25B- sold as 25I-NBOMe. J Med Toxicol 11:237–241. https://doi.org/10.1007/s13181-014-0445-9

Law R, Schier J, Martin C, Chang A, Wolkin A, Centers for Disease C (2015) Notes from the field: increase in reported adverse health effects related to synthetic cannabinoid use – United States, January–May 2015. MMWR Morb Mortal Wkly Rep 64:618–619

Lee HZS, Ong MC, Lim JLW, Yap TWA (2017) Challenges in GC-MS analysis: case studies on phenibut and ethylphenidate. Forensic Sci Int 277:166–178. https://doi.org/10.1016/j.forsciint.2017.06.002

Lemberger L, Rowe H (1975) Clinical pharmacology of nabilone, a cannabinol derivative. Clin Pharmacol Ther 18:720–726
Ling GS, Spiegel K, Lockhart SH, Pasternak GW (1985) Separation of opioid analgesia from respiratory depression: evidence for different receptor mechanisms. J Pharmacol Exp Ther 232:149–155
Listos J, Merska A, Fidecka S (2011) Pharmacological activity of salvinorin A, the major component of Salvia divinorum. Pharmacol Rep 63:1305–1309
Litjens RP, Brunt TM (2016) How toxic is ibogaine? Clin Toxicol (Phila) 54:297–302. https://doi.org/10.3109/15563650.2016.1138226
Liu L, Wheeler SE, Venkataramanan R, Rymer JA, Pizon AF, Lynch MJ, Tamama K (2018) Newly emerging drugs of abuse and their detection methods: an ACLPS critical review. Am J Clin Pathol 149:105–116. https://doi.org/10.1093/ajcp/aqx138
Lodge D, Mercier MS (2015) Ketamine and phencyclidine: the good, the bad and the unexpected. Br J Pharmacol 172:4254–4276. https://doi.org/10.1111/bph.13222
Lowe RH, Abraham TT, Darwin WD, Herning R, Cadet JL, Huestis MA (2009) Extended urinary Delta9-tetrahydrocannabinol excretion in chronic cannabis users precludes use as a biomarker of new drug exposure. Drug Alcohol Depend 105:24–32. https://doi.org/10.1016/j.drugalcdep.2009.05.027
Maas A, Madea B, Hess C (2018) Confirmation of recent heroin abuse: accepting the challenge. Drug Test Anal 10:54–71. https://doi.org/10.1002/dta.2244
MacDonald E, Arnesen TM, Brantsaeter AB, Gerlyng P, Grepp M, Hansen BA, Jonsrud K, Lundgren B, Mellegard H, Moller-Stray J, Ronning K, Vestrheim DF, Vold L (2013) Outbreak of wound botulism in people who inject drugs, Norway, October to November 2013. Euro Surveill 18:20630
Macher AM, Penders TM (2013) False-positive phencyclidine immunoassay results caused by 3,4-methylenedioxypyrovalerone (MDPV). Drug Test Anal 5:130–132. https://doi.org/10.1002/dta.1371
Martins SS, Sampson L, Cerda M, Galea S (2015) Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. Am J Public Health 105:e29–e49. https://doi.org/10.2105/AJPH.2015.302843
Matsumoto RR, Seminerio MJ, Turner RC, Robson MJ, Nguyen L, Miller DB, O'Callaghan JP (2014) Methamphetamine-induced toxicity: an updated review on issues related to hyperthermia. Pharmacol Ther 144:28–40. https://doi.org/10.1016/j.pharmthera.2014.05.001
McDonald R, Strang J (2016) Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction 111:1177–1187. https://doi.org/10.1111/add.13326
Mechoulam R (1970) Marihuana chemistry. Science 168:1159–1166
Mechoulam R (2000) Looking back at Cannabis research. Curr Pharm Des 6:1313–1322
Megarbane B, Chevillard L (2013) The large spectrum of pulmonary complications following illicit drug use: features and mechanisms. Chem Biol Interact 206:444–451. https://doi.org/10.1016/j.cbi.2013.10.011
Miliano C, Serpelloni G, Rimondo C, Mereu M, Marti M, De Luca MA (2016) Neuropharmacology of new psychoactive substances (NPS): focus on the rewarding and reinforcing properties of cannabimimetics and amphetamine-like stimulants. Front Neurosci 10:153. https://doi.org/10.3389/fnins.2016.00153
Minami M, Satoh M (1995) Molecular biology of the opioid receptors: structures, functions and distributions. Neurosci Res 23:121–145
Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sanchez E, Gutierrez-Rojas L, Meana JJ (2018) Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. CNS Drugs 32:411–420. https://doi.org/10.1007/s40263-018-0519-3
Morris H, Wallach J (2014) From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs. Drug Test Anal 6:614–632. https://doi.org/10.1002/dta.1620

Mowry JB, Spyker DA, Brooks DE, Zimmerman A, Schauben JL (2016) 2015 annual report of the American Association of Poison Control Centers' national poison data system (NPDS): 33rd annual report. Clin Toxicol (Phila) 54:924–1109. https://doi.org/10.1080/15563650.2016.1245421

Namera A, Kawamura M, Nakamoto A, Saito T, Nagao M (2015) Comprehensive review of the detection methods for synthetic cannabinoids and cathinones. Forensic Toxicol 33:175–194. https://doi.org/10.1007/s11419-015-0270-0

National Academies of Sciences E and Medicine (2017) The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. The National Academies Press, Washington

National Institute on Drug Abuse (NIDA) (2018) Overdose death rates. https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed 15 Nov 2018

O'Donnell JK, Halpin J, Mattson CL, Goldberger BA, Gladden RM (2017) Deaths involving fentanyl, fentanyl analogs, and U-47700 – 10 states, July-December 2016. MMWR Morb Mortal Wkly Rep 66:1197–1202. https://doi.org/10.15585/mmwr.mm6643e1

Odenwald M, al'Absi M (2017) Khat use and related addiction, mental health and physical disorders: the need to address a growing risk. East Mediterr Health J 23:236–244

Palamar JJ, Martins SS, Su MK, Ompad DC (2015) Self-reported use of novel psychoactive substances in a US nationally representative survey: prevalence, correlates, and a call for new survey methods to prevent underreporting. Drug Alcohol Depend 156:112–119. https://doi.org/10.1016/j.drugalcdep.2015.08.028

Palmateer NE, Hope VD, Roy K, Marongiu A, White JM, Grant KA, Ramsay CN, Goldberg DJ, Ncube F (2013) Infections with spore-forming bacteria in persons who inject drugs, 2000-2009. Emerg Infect Dis 19:29–34. https://doi.org/10.3201/eid1901.120044

Patrick ME, O'Malley PM, Kloska DD, Schulenberg JE, Johnston LD, Miech RA, Bachman JG (2016) Novel psychoactive substance use by US adolescents: characteristics associated with use of synthetic cannabinoids and synthetic cathinones. Drug Alcohol Rev 35:586–590. https://doi.org/10.1111/dar.12372

Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI (2016) Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. Clin Pharmacokinet 55:1059–1077. https://doi.org/10.1007/s40262-016-0383-6

Penninga EI, Graudal N, Ladekarl MB, Jurgens G (2016) Adverse events associated with flumazenil treatment for the management of suspected benzodiazepine intoxication – a systematic review with meta-analyses of randomised trials. Basic Clin Pharmacol Toxicol 118:37–44. https://doi.org/10.1111/bcpt.12434

Peters FT, Martinez-Ramirez JA (2010) Analytical toxicology of emerging drugs of abuse. Ther Drug Monit 32:532–539. https://doi.org/10.1097/FTD.0b013e3181f33411

Petrie M, Lynch KL, Ekins S, Chang JS, Goetz RJ, Wu AH, Krasowski MD (2013) Cross-reactivity studies and predictive modeling of "Bath salts" and other amphetamine-type stimulants with amphetamine screening immunoassays. Clin Toxicol (Phila) 51:83–91. https://doi.org/10.3109/15563650.2013.768344

Pettersson Bergstrand M, Helander A, Hansson T, Beck O (2017) Detectability of designer benzodiazepines in CEDIA, EMIT II Plus, HEIA, and KIMS II immunochemical screening assays. Drug Test Anal 9:640–645. https://doi.org/10.1002/dta.2003

Phillips KA, Hirsch GA, Epstein DH, Preston KL (2012) Cardiac complications of unwitting co-injection of quinine/quinidine with heroin in an intravenous drug user. J Gen Intern Med 27:1722–1725. https://doi.org/10.1007/s11606-012-2089-2

Pizon AF, Lynch MJ, Benedict NJ, Yanta JH, Frisch A, Menke NB, Swartzentruber GS, King AM, Abesamis MG, Kane-Gill SL (2018) Adjunct ketamine use in the management of severe ethanol withdrawal. Crit Care Med 46:e768–e771. https://doi.org/10.1097/CCM.0000000000003204

Presley CC, Lindsley CW (2018) DARK classics in chemical neuroscience: opium, a historical perspective. ACS Chem Neurosci 9:2503–2518. https://doi.org/10.1021/acschemneuro.8b00459

Prosser JM, Nelson LS (2012) The toxicology of bath salts: a review of synthetic cathinones. J Med Toxicol 8:33–42. https://doi.org/10.1007/s13181-011-0193-z

Regester LE, Chmiel JD, Holler JM, Vorce SP, Levine B, Bosy TZ (2015) Determination of designer drug cross-reactivity on five commercial immunoassay screening kits. J Anal Toxicol 39:144–151. https://doi.org/10.1093/jat/bku133

Richards JR, Hollander JE, Ramoska EA, Fareed FN, Sand IC, Izquierdo Gomez MM, Lange RA (2017) Beta-blockers, cocaine, and the unopposed alpha-stimulation phenomenon. J Cardiovasc Pharmacol Ther 22:239–249. https://doi.org/10.1177/1074248416681644

Roach JJ, Shenvi RA (2018) A review of salvinorin analogs and their kappa-opioid receptor activity. Bioorg Med Chem Lett 28:1436–1445. https://doi.org/10.1016/j.bmcl.2018.03.029

Rolland B, Jardri R, Amad A, Thomas P, Cottencin O, Bordet R (2014) Pharmacology of hallucinations: several mechanisms for one single symptom? Biomed Res Int 2014:307106. https://doi.org/10.1155/2014/307106

Ruiz-Colon K, Chavez-Arias C, Diaz-Alcala JE, Martinez MA (2014) Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: a comprehensive review of the literature. Forensic Sci Int 240:1–8. https://doi.org/10.1016/j.forsciint.2014.03.015

Safer DJ (2016) Recent trends in stimulant usage. J Atten Disord 20:471–477. https://doi.org/10.1177/1087054715605915

Sanger DJ (2004) The pharmacology and mechanisms of action of new generation, non-benzodiazepine hypnotic agents. CNS Drugs 18(Suppl 1):9–15; discussion 41, 43–45. https://doi.org/10.2165/00023210-200418001-00004

Satzinger G, Hartenstein J, Herrmann M, Heldt W (1975) Cyclic amino acids. US4024175A

Scheidweiler KB, Huestis MA (2014) Simultaneous quantification of 20 synthetic cannabinoids and 21 metabolites, and semi-quantification of 12 alkyl hydroxy metabolites in human urine by liquid chromatography-tandem mass spectrometry. J Chromatogr A 1327:105–117. https://doi.org/10.1016/j.chroma.2013.12.067

Schep LJ, Knudsen K, Slaughter RJ, Vale JA, Megarbane B (2012) The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol. Clin Toxicol (Phila) 50:458–470. https://doi.org/10.3109/15563650.2012.702218

Sena SF, Kazimi S, Wu AH (2002) False-positive phencyclidine immunoassay results caused by venlafaxine and O-desmethylvenlafaxine. Clin Chem 48:676–677

Shang Y, Filizola M (2015) Opioid receptors: structural and mechanistic insights into pharmacology and signaling. Eur J Pharmacol 763:206–213. https://doi.org/10.1016/j.ejphar.2015.05.012

Shulman J, Pizon A, Lynch M (2017) Trends in gabapentin abuse reported to poison centers, 2012-2015 (abstract). Clin Toxicol (Phila) 55:689–868. https://doi.org/10.1080/15563650.2017.1348043

Sieghart W (2015) Allosteric modulation of GABAA receptors via multiple drug-binding sites. Adv Pharmacol 72:53–96. https://doi.org/10.1016/bs.apha.2014.10.002

Simpson D, Braithwaite RA, Jarvie DR, Stewart MJ, Walker S, Watson IW, Widdop B (1997) Screening for drugs of abuse (II): cannabinoids, lysergic acid diethylamide, buprenorphine, methadone, barbiturates, benzodiazepines and other drugs. Ann Clin Biochem 34 (Pt 5):460–510. https://doi.org/10.1177/000456329703400502

Sinner B, Graf BM (2008) Ketamine. Handb Exp Pharmacol 182:313–333. https://doi.org/10.1007/978-3-540-74806-9_15

Skaugen JM, Scoccimarro A, Pizon AF, Rymer JA, Giannoutsos S, Ekins S, Krasowski MD, Tamama K (2019) Novel ketamine analogs cause a false positive phencyclidine immunoassay. Ann Clin Biochem 56:598–607. https://doi.org/10.1177/0004563219858125

Smith JP, Sutcliffe OB, Banks CE (2015) An overview of recent developments in the analytical detection of new psychoactive substances (NPSs). Analyst 140:4932–4948. https://doi.org/10.1039/c5an00797f

Smith RV, Havens JR, Walsh SL (2016) Gabapentin misuse, abuse and diversion: a systematic review. Addiction 111:1160–1174. https://doi.org/10.1111/add.13324

Solimini R, Rotolo MC, Pellegrini M, Minutillo A, Pacifici R, Busardo FP, Zaami S (2017) Adulteration practices of psychoactive illicit drugs: an updated review. Curr Pharm Biotechnol 18:524–530. https://doi.org/10.2174/1389201018666170710184531

Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA (2017) Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment-a systematic review. J Med Toxicol 13:71–87. https://doi.org/10.1007/s13181-016-0595-z

Spiller HA, Hays HL, Aleguas A Jr (2013) Overdose of drugs for attention-deficit hyperactivity disorder: clinical presentation, mechanisms of toxicity, and management. CNS Drugs 27:531–543. https://doi.org/10.1007/s40263-013-0084-8

Stankowski RV, Kloner RA, Rezkalla SH (2015) Cardiovascular consequences of cocaine use. Trends Cardiovasc Med 25:517–526. https://doi.org/10.1016/j.tcm.2014.12.013

Stanley TH (1992) The history and development of the fentanyl series. J Pain Symptom Manag 7: S3–S7

Stanley TH, Egan TD, Van Aken H (2008) A tribute to Dr. Paul A. J. Janssen: entrepreneur extraordinaire, innovative scientist, and significant contributor to anesthesiology. Anesth Analg 106:451–462, table of contents. https://doi.org/10.1213/ane.0b013e3181605add

Sternbach LH (1979) The benzodiazepine story. J Med Chem 22:1–7

Straseski JA, Stolbach A, Clarke W (2010) Opiate-positive immunoassay screen in a pediatric patient. Clin Chem 56:1220–1223. https://doi.org/10.1373/clinchem.2009.137596

Substance Abuse and Mental Health Services Administration (SAMHSA) (2018) Key substance use and mental health indicators in the United States: results from the 2017 National Survey on Drug Use and Health. In: US Department of Health and Human Services (ed)

Sugiura T, Waku K (2002) Cannabinoid receptors and their endogenous ligands. J Biochem 132:7–12

Suzuki J, Dekker MA, Valenti ES, Arbelo Cruz FA, Correa AM, Poklis JL, Poklis A (2015) Toxicities associated with NBOMe ingestion-a novel class of potent hallucinogens: a review of the literature. Psychosomatics 56:129–139. https://doi.org/10.1016/j.psym.2014.11.002

Szmuszkovicz J (1976) Analgesic n-(2-aminocycloaliphatic)benzamides. US4098904A

Tahara T, Araki K, Shiroki M, Matsuo H, Munakata T (1978) Syntheses and structure-activity relationships of 6-aryl-4H-s-triazolo[3,4-c]thieno[2,3-e] [1,4]diazepines. Arzneimittelforschung 28:1153–1158

Takayama H, Ishikawa H, Kurihara M, Kitajima M, Aimi N, Ponglux D, Koyama F, Matsumoto K, Moriyama T, Yamamoto LT, Watanabe K, Murayama T, Horie S (2002) Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. J Med Chem 45:1949–1956

United Nations Office for Drug Control and Crime Prevention (UNODCCP) (2001) Drug characterization and impurity profiling – background and concepts. United Nations Publication, New York

Van Lente F, Gatautis V (1998) Cost-efficient use of gas chromatography-mass spectrometry: a "piggyback" method for analysis of gabapentin. Clin Chem 44:2044–2045

van Wijk XMR, Yun C, Hooshfar S, Arens AM, Lung D, Wu AHB, Lynch KL (2018) A liquid-chromatography high-resolution mass spectrometry method for non-FDA approved benzodiazepines. J Anal Toxicol 43:316–320. https://doi.org/10.1093/jat/bky092

Volkow ND, Baler RD, Compton WM, Weiss SR (2014) Adverse health effects of marijuana use. N Engl J Med 370:2219–2227. https://doi.org/10.1056/NEJMra1402309

Vuckovic S, Prostran M, Ivanovic M, Dosen-Micovic L, Todorovic Z, Nesic Z, Stojanovic R, Divac N, Mikovic Z (2009) Fentanyl analogs: structure-activity-relationship study. Curr Med Chem 16:2468–2474

Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, Ruiz S, Ozonoff A (2013) Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ 346:f174. https://doi.org/10.1136/bmj.f174

Webster LR (2015) Opioid-induced constipation. Pain Med 16(Suppl 1):S16–S21. https://doi.org/10.1111/pme.12911

Weinstein AM, Rosca P, Fattore L, London ED (2017) Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health. Front Psych 8:156. https://doi.org/10.3389/fpsyt.2017.00156

Weissman A, Milne GM, Melvin LS Jr (1982) Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol. J Pharmacol Exp Ther 223:516–523

Wermeling DP (2015) Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Ther Adv Drug Saf 6:20–31. https://doi.org/10.1177/2042098614564776

Wiley JL, Marusich JA, Lefever TW, Antonazzo KR, Wallgren MT, Cortes RA, Patel PR, Grabenauer M, Moore KN, Thomas BF (2015) AB-CHMINACA, AB-PINACA, and FUBIMINA: affinity and potency of novel synthetic cannabinoids in producing delta9-tetrahydrocannabinol-like effects in mice. J Pharmacol Exp Ther 354:328–339. https://doi.org/10.1124/jpet.115.225326

Wilson MP, Pepper D, Currier GW, Holloman GH Jr, Feifel D (2012) The psychopharmacology of agitation: consensus statement of the american association for emergency psychiatry project Beta psychopharmacology workgroup. West J Emerg Med 13:26–34. https://doi.org/10.5811/westjem.2011.9.6866

Wong A, Little M, Caldicott D, Easton C, Andres D, Greene SL (2015) Analytically confirmed recreational use of Phenibut (beta-phenyl-gamma-aminobutyric acid) bought over the internet. Clin Toxicol (Phila) 53:783–784. https://doi.org/10.3109/15563650.2015.1059944

World Health Organization Department of Mental Health and Substance Abuse Management of Substance Abuse Team (NMH/MSD/MSB) Cannabis. https://www.who.int/substance_abuse/facts/cannabis/en/. Accessed 6 June 2019

Yogeeswari P, Ragavendran JV, Sriram D (2006) An update on GABA analogs for CNS drug discovery. Recent Pat CNS Drug Discov 1:113–118

Yuan J, Inami G, Mohle-Boetani J, Vugia DJ (2011) Recurrent wound botulism among injection drug users in California. Clin Infect Dis 52:862–866. https://doi.org/10.1093/cid/cir005

Zhu H, Wu LT (2016) Trends and correlates of cannabis-involved emergency department visits: 2004 to 2011. J Addict Med 10:429–436. https://doi.org/10.1097/ADM.0000000000000256

Zou S, Kumar U (2018) Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci 19:833. https://doi.org/10.3390/ijms19030833