Pharmacodynamic Evaluation: Drug Dependency and Addiction

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F. J. Hock, M. R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-56637-5_49-1

Abstract

The intake of psychoactive substances has accompanied mankind since the dawn of human race. Different psychoactive substances have been extracted and synthesized in human history, and their pharmacodynamic properties have been studied thoroughly. This review presents the current knowledge on the pharmacodynamic profile of the most common illicit and recreational drugs and its influence on drug dependency and addiction. The substances with abuse potential grow exponentially. Our clinical and practical knowledge has still a long way to go in catching up with these realities. The dynamic interactions between different drugs observed in vitro cannot be fully replicated in vivo. We rely on randomized clinical trials, case reports, and own clinical experience with patients. Different clinical scenarios could provide further evidence and hypotheses regarding the sought and adverse effects of substances, their interactions with legal drugs and medications, and their impact on different stages of metabolism. In this chapter we attempted to summarize the available reliable data and suggest some ideas for future observation and research.

Introduction

Pharmacodynamics is a branch of pharmacology that studies the molecular, biochemical, and physiological effects and the mechanisms of action of a substance (i.e., a drug) on the human body (Campbell and Cohall 2017). All substances that affect the human body either influence normal biochemical or physiological processes or inhibit the vital processes of an "invader" to the body – microorganism or parasite. On molecular level, overall seven major mechanisms of drug action have been described in the human body:

- Stimulation/activation of receptor systems (agonism, e.g., beta-agonists in asthma)
- Inhibition/depression of receptor systems (antagonism, e.g., calcium channel blockers in hypertension)
- Blocking of receptors without further activation or inhibition ("silent" antagonism, e.g., naloxone in opioid intoxication)
- Stabilization of receptors (e.g., buprenorphine in opioid dependency)
- Exchange of substances (e.g., digitalis glycosides, anesthetics, etc.)
- Initiation/activation of beneficial chemical reactions (acetyl cysteine as initiator of free radical scavenging)
- Initiation/activation of harmful chemical reactions (e.g., cytotoxic treatment)

Pharmacodynamics of a substance comprises of three major types of processes: (1) binding to structures (receptors) in the body and resulting in desired and undesirable (adverse) effects, (2) post-receptor effects, and (3) interactions with other substances within the body. The binding to certain structures within the body (receptors, membrane structures, proteins, enzymes, ion pimps, etc.) leads to further molecular, biochemical, and physiological effects. The difference between the doses leading to desired effects and the one that leads to adverse events is the therapeutic window of a drug. The duration of action of a drug is the length of time that the drug remains effective. From pharmacodynamic point of view, the receptor binding, the therapeutic and adverse effects, the therapeutic window, and the duration of action in drug dependency and addiction depend mainly on the receptor target, the properties of the drug itself and the dose taken, and the concentration of the drug at the receptor site and on certain physiological changes in the body (aging, intake of other substances/drugs, genetic polymorphisms and conditions, metabolic disturbances [thyrotoxicosis, malnutrition, renal or hepatic failure, dyselectrolytemia, etc.]). Moreover, the

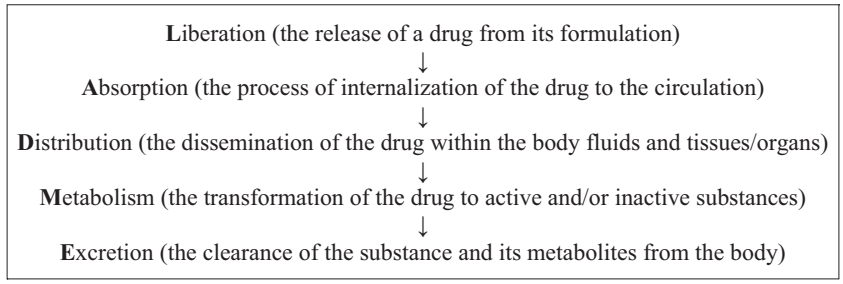

Fig. 1 LADME scheme of a pharmacokinetic profile of a drug

concomitant abuse of several substances, including alcohol and prescription medications, could potentiate the effects of illicit drugs due to pharmacodynamic (and pharmacokinetic) interactions. All these factors alter the pharmacodynamics of illicit and recreational drugs and modify the profile of dependency, addiction, and withdrawal.

On the other hand, pharmacokinetics studies the effects of the body on the drug: drug absorption, distribution, metabolism, and excretion (Ruiz-Garcia et al. 2008). The pharmacokinetic profile of a drug can be presented schematically in the so-called LADME sequence (Ruiz-Garcia et al. 2008) (Fig. 1). Sometimes the terms metabolism and excretion are grouped together in the term "elimination."

In terms of drug abuse and dependence, pharmacodynamics and pharmacokinetics are often referred to as toxodynamics and toxokinetics because of the toxic effects of illicit drugs and the high rate of adverse and toxic reactions in this patients' population.

The pharmacodynamic and the pharmacokinetic profiles of illicit and recreational drugs define their effects, adverse reactions, addiction, and withdrawal symptoms. In general, the illicit drugs with more rapid absorption and entry into the circulation and the central nervous system, higher bioavailability, shorter half-life, high free drug levels, smaller volume of distribution, and higher clearance rate are more toxic and tend to cause higher rate of addiction and more severe withdrawal symptoms. Most of the drug users tend to adapt the route of administration, the dose and the additives, and/or the coadministered illicit drugs with additive/synergistic effects to their individual cravings in order to produce maximum drug effect for maximum time.

Before we start discussing the pharmacodynamics of addictive substances, we have to answer the following important questions: Which substances actually make us feel happy, and which parts of the brain give the signals of happiness? The substances that make us feel happy are physiological mediators in the brain that are secreted in response to a stimulus giving us the sensation of comfort or reward. These are the endorphins, serotonin, dopamine, and oxytocin. The physiological sites where these stimuli act are the limbic system (and particularly nucleus accumbens), the memory/experience part of the brain (hippocampus and amygdala), and the cortex (the frontal and prefrontal areas that supervise the first two parts stated) (Powledge 1999; Volkow and Morales 2015). This "reward pathway" in the brain is a very ancient dopaminergic pathway that was present long before humans in the brain of mammals. It plays crucial role for the motivation of behavior. It starts in the midbrain (in the ventral tegmental area) and extends to nucleus accumbens, hippocampus, amygdala, and the prefrontal and frontal cortical areas that are meant to inhibit all the structures before them in the pathway (Powledge 1999; Volkow and Morales 2015). After disinhibition of the subcortical structures, a vicious circle of constant "reward" stimulation is closed ("the reward cycle").Virtually all illicit drugs follow this pathway of addiction, along with nicotine, caffeine, and alcohol (Powledge 1999). This neuromediator pathway is stimulated not only by

natural stimuli (success, victory, self-content from the achieved, etc.) but by stimulant medications and addictive types of self-destructive behavior, including eating disorders and gambling (Powledge 1999; Volkow and Morales 2015).

All addictive substances tend to bind specific receptors in the brain that lead to liberation of serotonin, dopamine/norepinephrine, and/or oxytocin and therefore to imitate the state of comfort and/or the reward ensured by other natural stimuli in our everyday life, but the artificially induced state of happiness and/or excitement is more intense. Still, the administration of recreational drugs leads to structural and functional changes in neurons, called neuroplasticity. These adaptive changes alter the drug effect and metabolism and generate the need for more frequent administration in higher doses, which is called tolerance with further dependence and addiction. The sudden cease in drug intake leads to withdrawal symptoms. Withdrawal symptoms are often mediated by dopaminergic pathways and/or by extrahypothalamic corticotropin-releasing factor (CRF) system – release of CRF outside the hypothalamus (e.g., from the amygdala). This could explain the common withdrawal symptoms (sweating, changes in blood pressure and heart rate, abnormal peristaltics, joint pains, headache, etc.) for different illicit drugs, including opiates, stimulants, alcohol, nicotine, cannabinoids, etc.

In other words, the majority of psychoactive substances tend to bind specific receptor in the central nervous system (CNS) and to mimic the effects of endogenic substances with the effect being more potent and with longer duration: opioid, benzodiazepine/gamma-aminobutyric acid (GABA), serotonin, dopamine, and cannabinoid receptors (Quinn et al. 1997; Sharma et al. 2012). Moreover, these receptors are known to interact and to lead to a neurochemical correlation between substances abused within the brain (Quinn et al. 1997). Stimulant drugs (cocaine, amphetamines, and amphetamine derivatives) act by causing an increase in dopamine levels within the synaptic cleft – by facilitating dopamine release and inhibiting dopamine reuptake (Nestler 2005; Calipari and Ferris 2013). Cocaine also blocks sodium channels on cell membranes and has anesthetic effect (Volkow and Morales 2015). Nicotine activates *N*-cholinergic receptors and is known to stimulate catecholamine (dopamine, norepinephrine), glutamate, serotonin, acetylcholine, endorphin, and GABA release (Quinn et al. 1997; Benowitz 2009). Moreover, its primary metabolite, cotinine, is known to increase serotonin levels in the brain (Quinn et al. 1997). Only alcohol has no specific receptors in the brain and acts by altering the physiological properties of lipid membranes, modifying their fluidity and changing the receptor sensitivity to natural stimulant, and inhibiting neurotransmitters (Quinn et al. 1997).

As it was stated above, the changes in the human body in response to the intake of substances, especially in receptor systems and signaling pathways in the brain, are referred to as plasticity (respectively, neuroplasticity). These changes are responsible for the development of tolerance, i.e., the need for more frequent administration of the addictive substance and in higher doses. Once this need evolves to imperative urge, an addiction has developed. From pharmacodynamic point of view, the major mechanisms underlying neuroplasticity are as follows: changes in receptor structure, type, distribution, and functionality, changes in signaling pathways, development of tolerance and cross-tolerance, involvement of other receptor pathways due to the cross-reaction between receptor systems, and development of new pathways for signal channeling (Dumas and Pollack 2008).

Moreover, all addictive substances used for recreational purposes are known to cause permanent structural alteration in cells due to epigenetic and genetic effects, including microtubular toxicity, chromothripsis, genotoxicity, oncogenesis and embryo-/fetotoxicity, inhibition of tumor-suppressor genes (e.g., p53 by marijuana smoke) and activation of proto-oncogenes, etc. (Reece and Hulse 2016). The major mechanism behind the inheritable genetic abnormalities in illicit substance abuse is thought to be the process of chromothripsis – extensive genomic rearrangements and an oscillating pattern of DNA copy number levels due to microtubular damage and changes in the mitotic spindle. These alterations are curiously restricted to one

or a few chromosomes. All illicit drugs are known to cause changes in sister chromatid exchange levels, in the mitotic spindle, in DNA fragmentation, and in gene systems that regulate the cell processes (including growth and development) (Dumas and Pollack 2008; Reece and Hulse 2016; Li and Lin 1998; Reece 2009). Having in mind the wider prevalence of illicit drug intake worldwide, the possibilities for transgenerational genotoxicity (terato- and oncogenicity and toxicity) raise serious and increasing concern (Benowitz 2009).

A very important aspect of both pharmacodynamics and pharmacokinetics of illicit drugs are the drug interactions that determine the potentiation or inhibition of effect and the possibilities to influence withdrawal and cessation of illicit drug abuse by the administration of their analogues or medications that block their action or ameliorate abstinence symptoms.

Pharmacodynamic profiles of commonly abused drugs and their significance for the treatment of withdrawal and addiction.

Opioids

The term "opiate" refers to a substance derived from opium, i.e., the alkaloids found in the plant *Papaver somniferum* (opium poppy). Three main psychoactive compounds are isolated from this plant – morphine, codeine, and thebaine – along with several alkaloids that lack psychoactive properties and have only spasmogesic effect (papaverine, noscapine, and about 24 more substances). Other morphine-like substances that have been isolated in small amounts from the opium poppy are dihydrocodeine, metopon, oxycodone, and oxymorphol.

The term "opioids," on the other hand, includes a large group of substances that interact with the opioid receptors in a morphine-like way, producing analgesic, anesthetic, and psychoactive effects. Opioids have been familiar to humans for thousands of years for their analgesic and psychoactive properties. These substances are widely used for recreational purposes, including their euphoric, hallucinogenic, and other psychoactive effects. In 2013 up to 0.8% of the population aged 15–65 years worldwide reported using opioids for recreational purposes (Status and Trend Analysis of Illicit Drug Markets 2015). Their rewarding effects, explained by activation of dopaminergic pathways in the "reward cycle" of the brain (including parts of the limbic system), are the main cause of opioid abuse, addiction, and dependence. Severe withdrawal symptoms develop in abrupt drug cessation; therefore proactive treatment is needed.

According to their presence in nature, opioids are classified in several groups (Ghelardini et al. 2015; Koob and Le Moal 2006):

- Natural – morphine, codeine, thebaine, and salvinorin A (kappa-agonist)
- Morphine esters – morphine diacetate (heroin), morphine dinicotinate, morphine dipropionate, etc.
- Semisynthetic (created from natural opiates or their esters) – hydromorphone, hydrocodone, oxymorphone, oxycodone, buprenorphine, ethylmorphine, etc.
- Synthetic – fentanyl, methadone, tramadol, tapentadol, dextropropoxyphene, pethidine, levorphanol, etc.
- Endogenic – endorphins, enkephalins, dynorphins, and endomorphins

The adverse effects of opioid abuse include cognitive impairment, gastrointestinal symptoms (constipation, nausea, vomiting), hypotension, sexual dysfunction, and respiratory and cardiovascular center depression.

Three major types of opioid receptors have been identified and cloned: mu, delta, and kappa. An additional opioid substance binding type of receptor is the ORL-1 (opioid receptor-like 1, or nociceptin receptor). Three additional types of opioid ligand binding receptors have been discovered – zeta and epsilon opioid receptors and sigma receptors. All types of opioid receptors have different distributions and physiological roles (Ghelardini et al. 2015; Koob and Le Moal 2006; Stein et al. 2003; Gosnell et al. 2013):

- Mu: distributed in the brain (cortex, thalamus, striosomes, periaqueductal gray matter, rostral ventromedial medulla), in the spinal cord, in the peripheral sensory neurons, and in the gastrointestinal tract and other peripheral structures. Subtypes: mu1 (analgesia, dependence), mu2 (euphoria, miosis, respiratory and gastrointestinal motility depression, physical dependence), and mu3 (vasodilation?).
- Kappa: distributed in the brain (hypothalamus, periaqueductal gray matter, claustrum), spinal cord, and peripheral sensory neurons. Subtypes: kappa1, kappa2, and kappa3, responsible for analgesic, depressive, hallucinogenic, miotic, diuretic, dysphoric, neurodepressive, sedative, and neuroprotective effects.
- Delta: distributed in the brain (deep cortex, pontine nuclei, amygdala, olfactory bulb) and peripheral sensory neurons. Subtypes: delta 1 and delta 2, responsible for analgesic and antidepressant effects, convulsogenic properties, and dependence.
- ORL-1 (nociceptin receptor): distributed in the brain (amygdala, hypothalamus, hippocampus, cortex, septal nuclei) and the spinal cord. Responsible for anxiety, depression, appetite changes, and dependence to mu-agonists and affects both pain and reward signaling within the brain.
- Epsilon (binding beta-endorphin): distributed in the brain and peripheral sensory neurons, probably a splice variant or a heteromer of existing opioid receptors, antagonized by buprenorphine. Responsible for analgesic effect and for the release of met-enkephalin.
- Sigma: referred to as antitussive receptors, binding 4-phenyl-1-(4-phenylbutyl) piperidine and other substances (including dextromethorphan, phencyclidine, cocaine and methamphetamine, morphine and diacetyl morphine, fluvoxamine, dimethyltryptamine, etc.). Known to interact with kappa-opioid and NMDA glutamate receptors. Known two subtypes – sigma1 and sigma2 (sigma1 having no structural similarity to the opioid receptors). Their activations mimic acute stress reactions – tachycardia, mydriasis, overall stimulation, antitussive effect, and euphoria/dysphoria. Sigma-receptors bind to several hormones – dehydroepiandrosterone and gestagens.
- Zeta (opioid growth factor receptor): distributed in peripheral tissues (parenchymal organs – heart, liver, kidney, brain, pancreas, fat tissue, and skeletal muscles). Responsible for tissue growth, embryonic/fetal growth, wound healing, and development and cancer proliferation. The activation of these receptors decreases cell proliferation (i.e., acts as "negative" growth factor).

Opioid receptors are abundant in all tissues and organs, including the brain, peripheral nerves, gastrointestinal and immune system, endocrine glands, and skin, where they have different analgesic and non-analgesic physiological effects, as described above. All opioid receptors represent G protein-coupled receptors acting via changes (decrease) in adenylate cyclase activity and cAMP levels, protein kinase activity, CREB protein, and calcium and potassium ion transport. Moreover, the activation of opioid receptors leads to changes in substance P and GABAergic, glutamatergic, and dopaminergic transmission, leading to decrease in pain sensation and psychoactive properties, including activation of the reward cycle and euphoria (Quinn et al. 1997; Ghelardini et al. 2015; Koob and Le Moal 2006; Stein et al. 2003; Gosnell et al. 2013; Pasternak and Pan 2013). Tramadol and tapentadol also affect monoamine uptake (Quinn et al. 1997; Ghelardini et al. 2015; Koob and Le Moal 2006; Stein et al. 2003; Gosnell et al. 2013; Pasternak and Pan 2013). Opioid agonists (mu, kappa, and delta) are known to interact with oxytocin, neuropeptide Y, and melanocyte-stimulating hormone signaling systems (Gosnell et al. 2013; Pasternak and Pan 2013), which could explain their effects on feeding and appetite.

According to their effect on opioid receptors, the ligands can be classified as agonists, antagonists, partial agonists, and mixed agonists/antagonists:

- Agonists – bind strongly to opioid receptor and undergo strong conformational changes to

exert effect: morphine, heroin, hydrocodone, hydromorphone, fentanyl, methadone, oxycodone, and oxymorphone.
- Partial agonists – bind less strongly and cause less conformational changes with less receptor activation and at low doses cause similar analgesic effects like full agonists; increasing the dose does not increase analgesic activity: buprenorphine, tramadol, and butorphanol.
- Mixed agonists/antagonists – agonists to some and antagonists to other opioid receptors and dose-dependent effect (i.e., agonists at some and antagonists on other doses): buprenorphine, butorphanol, nalbuphine, and pentazocine. For instance, buprenorphine is a partial mu-agonist and kappa-antagonist and weak delta-antagonist; butorphanol is a mu-antagonist and partial kappa-agonist, pentazocine is a partial mu-agonist and kappa-agonist, and nalbuphine is a mu-antagonist and kappa-agonist.
- Antagonists: naloxone and naltrexone.

To make the long story short, most psychoactive opioids are mu-agonists with different actions on kappa-receptors. As described above, the activation of mu-opioid receptors leads to G protein-mediated decrease of adenylate cyclase activity and inhibition of cAMP production with subsequent inhibition of calcium influx and potassium efflux with membrane hyperpolarization and analgesic effect. Moreover, these substances change the levels of substance P and GABAergic, glutamatergic, and dopaminergic transmission with suppression of pain signaling and activation of the reward cycle. In addition, many synthetic opioids have supplementary effects (i.e., inhibition of norepinephrine uptake and NMDA receptor inhibition with increased glutamate and GABA signaling), so other signal systems in the brain are also used to mediate their psychoactive effects (Koob and Le Moal 2006; Gosnell et al. 2013; Pasternak and Pan 2013).

Pharmacological Effects

Mu-receptor opioid agonists have the following pharmacological effects (Ghelardini et al. 2015; Koob and Le Moal 2006):

- Analgesic – mediated by mu-opioid receptors (at spinal and supraspinal levels). This effect is a result of complex ion- and mediator-induced changes in neuron interactions. At supraspinal level, it is a result of activation of mu-receptors on GABAergic neurons with subsequent activation of serotoninergic neurons. At spinal level, this effect is due to increase in the pain threshold and is mediated by inhibition of the release of mediators participating in the pain signaling – substance P and glutamate and nitric oxide from the nociceptive afferent neuron cells. Methadone also interacts with the mu-receptors on glutamatergic neurons and thus additionally decreases the transmission of the pain signal. Mesangial cells are also known to have opioid receptors which at least partially can explain the development of heroin-associated nephropathy.
- Psychotropic effects – these effects are mediated by the opioid receptors on structures of the limbic system, including the cortical areas, hypothalamus, locus coeruleus, and amygdala.
- Effects on respiratory functions – mediated by the opioid receptors in the brainstem, along with miosis.
- Gastrointestinal effects (decreased mobility, suppressed nausea) – via the opioid receptors on peripheral neurons and on the gastrointestinal tract.
- Respiratory effects – suppression of cough, in larger doses, and suppression of breathing.
- Endocrine effects (via hypothalamic mu-receptors with subsequent suppression of pituitary functions) – inhibition of pituitary function with decreased levels of LH, FSH, and ACTH.
- Paradoxical effects of morphine – at low doses morphine can increase the sensation of pain – hyperalgesia, probably due to activation of pronociceptive mediation via stimulation (not inhibition) of adenylate cyclase and increase in

neuron excitability. This effect is dose-dependent.

The development of tolerance and addiction is explained by several phenomena, including decrease in receptor number and affinity and internalization of receptors and changes on post-receptor level that decrease the ligand effect and lead to the need of more frequent administration of higher doses. The withdrawal symptoms of opioid dependence are very unpleasant and further increase the craving. They are mediated via changes in adrenergic and cholinergic mediation and neuropeptide Y changes in CRF receptor system (Koob and Le Moal 2006). According to their severity, these symptoms can be classified into 5 grades (from 0 to 4) (Koob and Le Moal 2006):

- Grade 0 – craving (for the drug) and anxiety
- Grade 1 – grade 0 plus yawning, increased perspiration, runny nose, and lacrimation
- Grade 2 – grade 0 and 1 with increased intensity plus sympathetic activation (mydriasis, gooseflesh with piloerection ("cold turkey detox"), marked tremor and twitches/spasms, hot and cold flushes); severe pain in the joints, bones, and muscles; and loss of appetite
- Grade 3 – all of the above, with increased intensity, plus insomnia, signs of sympathetic activation (increased blood pressure, body temperature, heart and respiratory rate, restlessness, muscle twitches), and nausea
- Grade 4 – all of the above, with increased intensity, plus vomiting, diarrhea, loss of appetite, weight loss, embryonic position, spontaneous ejaculation/orgasm, dehydration with hemoconcentration and eosinopenia, and high blood glucose

These symptoms can be alleviated with the administration of beta-blockers, sedatives, and antipsychotics, supportive treatment (hydration, parenteral feeding, gastroprotective agents, etc.), and addition of morphine analogues (Quinn et al. 1997; Pasternak and Pan 2013).

Natural Opioid-Like Substances

Several endogenic substances mimic the effects of opioid and are classified as endogenous opioids (Ghelardini et al. 2015; Pasternak and Pan 2013):

- Enkephalins (pentapeptides containing the sequence Tyr-Gly, linked to leucine or methionine and called, respectively, leu-enkephalin and met-enkephalin) – bind predominantly to kappa-receptors.
- Dynorphins A and B – bind mainly to delta-receptors.
- Endorphins – the beta-endorphins bind equally to mu- and delta-receptors.
- Endomorphin-1 and endomorphin-2 – bind mainly to mu-receptors.
- Endogenous morphine synthesis has been proven in humans and in animals, but the role of this "animal" morphine and its precursors and derivatives remains unclear.

All these substances take part in the pain and reward signaling, both central and peripheral, but their exact role in human physiology remains unclear.

Several peptides have been shown to modulate opioid action, including cholecystokinin and neuropeptide FF that reduce opioid effects (Mollereau et al. 2005) via changes in intracellular second messengers of nociception. The pronociceptive opioid analogues nociceptin and dynorphin (Mollereau et al. 2005) paradoxically are able not only to potentiate but also to attenuate the analgesic effects of opioids due to changes in pain circuit signaling.

Pharmacologic Interactions of Opioids

The epidemic of opioid prescription abuse makes it even more important to focus our clinical attention on their drug interactions. Methadone and buprenorphine, as with most of the psychoactive medications, are substrates of CYP450 3A4. The hepatic metabolism of opioids also goes through other isoenzymes from the CYP family, such as 2B6, CYP2C19, CYP2C9, and CYP2D67 for

methadone and 2C8 for buprenorphine. A classical interaction would be a strong 3A4 inhibitor (e.g., ketoconazole) increasing the plasma levels of methadone. Same interaction could be observed with an antifungal and an antibiotic – ciprofloxacin. Per FDA criteria, strong inhibition leads to fivefold and higher increase of the plasma concentration of the inhibited substrate. On the other hand, inducing strongly CYP450 system would lead to lower plasma level of its substrates. However, the correlations are not always that linear. One of the reasons is the influence of medications on the glucuronidation. Methadone inhibits glucuronidation of zidovudine, thus decreasing its elimination and increasing the risk of toxicity (McCance-Katz et al. 1998). There are several important class interactions: (1) opioids with medications treating infectious diseases (HIV, tuberculosis, Hep C, etc.), (2) opioids with psychopharmacologic agents (antidepressants, antipsychotics, benzodiazepines), and (3) opioids with alcohol or illicit substances.

Three types of consequences due to interactions:

1. **Toxicity**, **higher rate, and more severe side effects** – related to slowing the rate of metabolism/elimination, increasing the plasma levels of:
   (a) The concomitant drugs administered with opioids, e.g., zidovudine (lactic acidosis, transaminitis, myopathy, severe anemia or neutropenia, etc.)
   (b) Opioids, e.g., methadone (cognitive dysfunction, respiratory depression, QTc prolongation, arrhythmias) with cotreatment with azoles and ciprofloxacin *or* discontinuation of CYP450 inducers (such as carbamazepine, phenytoin, phenobarbital)
   (c) Synergistic and pharmacodynamic effects: Increased sedation, delirium, and respiratory drive (opioids with alcohol, benzodiazepines, antihistamine medications (diphenhydramine), dextromethorphan)
2. **Poor therapeutic response to concomitant drugs –** Related to increased rate of metabolism/elimination of antiretrovirals and poor efficacy. Complications: viral mutations, antiretroviral resistance, and increased risk for viral transmission (lower concentrations of didanosine and stavudine)
3. **Opioid withdrawal**
   (a) Related to increased rate of metabolism/elimination of opioids (methadone, buprenorphine), e.g., **HIV medications (**efavirenz, nelfinavir, lopinavir/ritonavir, etc.), **tuberculosis medications** (rifampin), **anticonvulsants** (carbamazepine, phenytoin, phenobarbital), and **stimulants (**cocaine (CYP3A4, P), glycoprotein inducer)
   (b) Discontinuation or lowering the dose of CYP450 inhibitors, medications which increase the plasma concentrations of opioids (fluvoxamine, fluoxetine) and antibiotics (incl azoles)
   (c) Pharmacodynamic interactions – Cocaine during sublingual use of buprenorphine (vasoconstriction)

Drug Interactions for Specific Opioids

See Table 1

Interactions with Clinical Importance

Morphine delays the absorption of clopidogrel, prasugrel, and ticagrelor and enhances gabapentin pain tolerance in healthy volunteers. Quinidine can enhance the activity of opioids – morphine, fentanyl, oxycodone, codeine, dihydrocodeine, and methadone. Antimycotic medications increase the plasma concentrations of opioids – buprenorphine, fentanyl, morphine, oxycodone, methadone, tilidine, and tramadol. Protease inhibitors induce metabolism of opioids – oxycodone and fentanyl. Paroxetine inhibits the metabolism of hydrocodone, oxycodone, and tramadol. Escitalopram inhibits the metabolism of tramadol (Feng et al. 2017).

Stimulants: Cocaine and Amphetamine and Its Derivatives

All psychostimulants act by increasing monoamine (norepinephrine, dopamine, and serotonin) release in the synaptic space and by inhibiting

Table 1

Opioid	**Morphine**			
	↑ own concentration – **toxicity**	↑ the other agent's concentration toxicity	↓ the other agent's concentration	↓ own concentration – **withdrawal**
Absorption	Metoclopramide	P2Y12 inhibitors Gabapentin		Rifampin
Metabolism Elimination	Quinidine Itraconazole Other azoles Amantadine			Rifampin St. John's wort
	Methadone			
Absorption	Quinidine Voriconazole Ketoconazole Grapefruit juice	AZT (zidovudine) Desipramine		Rifampin
Metabolism	Delavirdine Amitriptyline Dextromethorphan Quetiapine Ciprofloxacin		Didanosine, stavudine	Darunavir Efavirenz Nelfinavir Nevirapine Lopinavir/ritonavir Carbamazepine Phenytoin Phenobarbital
	Buprenorphine			
Metabolism	Antimycotics			Carbamazepine Phenytoin Phenobarbital
	Oxycodone			
	Antimycotics Macrolides Ketolides Protease inhibitors Voriconazole Ketoconazole Grapefruit juice Paroxetine Quinidine			

their reuptake leading to increased neurotransmitter levels for a longer time in the synaptic cleft (Quinn et al. 1997).

Cocaine

Cocaine is the second most frequently used recreational drug worldwide after cannabis. It is a natural alkaloid extracted from the leaves of the coca plant (*Erythroxylum coca* var. *coca*, var. *ipadu*, var. *novogranatense*, and var. *truxillense*), growing in South America. Cocaine can be extracted from coca leaves or synthesized and used as a recreational substance, or further processed to crack cocaine – a freebase form of cocaine that can be smoked. Between 14 and 21 million people are estimated to have used this drug every year (Pomara et al. 2012).

Cocaine has been used for more than 1000 years by the indigenous South American people as a stimulant and for religious and recreational purposes in the form of *Erythroxylum coca* leaves that can be chewed or processed to extract the alkaloid. There are proofs that cocaine has been used as anesthetic in ancient times (Gay et al. 1975). In the seventeenth century when the Spanish arrived to the New World, they described

the stimulant, hunger-suppressing, anesthetic, and recreational effects of coca leaves. The alkaloid was first isolated by Friedrich Gaedcke in 1855 and was initially named erythroxyline. Approximately 40 years later, in 1989, the first synthetic cocaine appeared. The drug was initially used as a painkiller; subsequently its local anesthetic properties were used. Cocaine was found to be a unique anesthetic because unlike all other anesthetics it decreased bleeding due to its local vasoconstriction effect. In 1879 cocaine was introduced for the treatment of morphine addiction, and in the next few year, its use as a psychostimulant and appetite-suppressing drug started. In the beginning of the twentieth century, it was marketed as stimulant and was subsequently used in world wars as stimulant and anesthetic. Gradually, cocaine has become the second most abused illicit drug worldwide. It is used by all socioeconomic strata, age, and demographic, economic, social, political, and religious groups all over the world. Cocaine can be insufflated (snorted), taken orally (gingival administration and chewing coca leaves), smoked, administered rectally, and injected intravenously or intramuscularly. It can be taken alone or in combination with heroin (speedball). In modern medicine its use is limited as local/topical anesthetic, mainly in ophthalmology.

Cocaine has sympathomimetic effects, influencing serotonin receptor and membrane ion transport. Cocaine is also known to have long-term endocrine and genetic effects.

The pharmacodynamic effects of cocaine are determined by its three major actions (Quinn et al. 1997; Pomara et al. 2012; Gay et al. 1975):

- Increased release of catecholamines in the synaptic cleft due to stabilization of the dopamine transporter
- Decreased mediator reuptake via blockage of the presynaptic dopamine transporter
- Blockage of neuronal membrane sodium channels with local anesthetic effect

Additionally, cocaine interacts with serotonin 5-HT3 and 5-HT2 receptors, and these interactions explain its effect on appetite and locomotion. The effects on locomotion could also be explained by its interaction with dopamine levels in the substantia nigra.

Cocaine also interacts with kappa-opioid, sigma, D1, and NMDA receptors.

Unlike amphetamine, cocaine *does not* inhibit monoamine oxidase (MAO) (Quinn et al. 1997).

The net effect of these ligand-receptor interactions is sympathomimetic effect with buildup of dopamine in the limbic system structures (especially in the nucleus accumbens) and stimulation of pleasure and reward feeling that explains the addiction and dependence in long-term abuse (Nestler 2005). The increase of dopamine levels in the nucleus accumbens is a normal physiological process, part of the fight-or-flight response to stress, giving the body and the mind the assurance that the stress-inducing stimulus has been eliminated and generating the sensation of comfort and pleasure – i.e., when a thirsty person drinks water, or when a reward for achievement has been given (Nestler 2005). Thus, the external stimulation and the buildup of dopamine levels in the nucleus accumbens by cocaine are far more potent than the physiological effect and give the sensation of euphoria and stimulation. This is the underlying mechanism of addiction and dependence. Cocaine also exerts its dopamine buildup effects in other regions of the brain, associated with the limbic system, including memory centers (hippocampus and amygdala) and the frontal cortex. It is believed that the repeated exposure to cocaine with increase in dopamine availability in the hippocampus and amygdala leads to functional and organic changes that every memory of cocaine intake urges an almost compulsory craving for repeated intake (Volkow and Morales 2015). The repeated increase in dopamine levels in the frontal cortex by cocaine abuse is associated with changes in this region and decrease of its inhibitory effect over the urges generated in the nucleus accumbens, hippocampus, and amygdala and subsequent addictive pattern.

The interactions with serotonin receptors may explain the mood and appetite-suppressing effects of cocaine.

A more serious molecular effect that can explain the addiction in cocaine intake is the genetic impact of this alkaloid. Cocaine is known to change the amount of dopamine transporters and dopamine receptors on nerve cells via alteration of gene expression (genetic effects of cocaine). ΔFosB is a natural protein substance present in small amount in nerve cells, especially in the nucleus accumbens. It plays a role in the genetic mechanisms of the basic cell functions – the integrity and the interaction with other cells. In chronic cocaine intake, this protein accumulates in large quantities in the nucleus accumbens and is thought to be the part of the mechanisms explaining the addiction to cocaine. Changes in ΔFosB levels in the nucleus accumbens have been demonstrated in long-term cocaine intake in mouse models. It is known that one of the genes stimulated by ΔFosB, the enzyme cyclin-dependent kinase 5 (CDK5), promotes nerve cell growth. This factor also affects nuclear factor-kappa B and MEF2 (myocyte enhancer factor-2) expression. These effects are not well understood. It has been speculated that probably these transcriptional and epigenetic changes could be the genetic mechanism of the very long-term effects of cocaine. In a very long term, intake of cocaine increased dendrite growth and increases the number of the neurons in the nucleus accumbens that has been observed, i.e., increased cell contacts with other parts of the nervous system with altered information pathways and increased amount of signals coming to and originating from these cells with stable behavioral changes (Volkow and Morales 2015; Robison and Nestler 2011). These very long-term effects, based on genetic and epigenetic changes in the brain, probably make cocaine addiction very difficult to counteract. Another long-term effect of cocaine is dopamine depletion that is probably responsible for withdrawal symptoms (Quinn et al. 1997).

The main medical strategies to treat cocaine addiction and withdrawal are (Quinn et al. 1997) the following: the use of antidepressants (in order to inhibit neurotransmitter reuptake, particularly desipramine), dopamine agonists (to counteract dopamine depletion in the central nervous system), dopamine antagonists, anticonvulsants, and opioids (buprenorphine – probably through affecting the linkage between opioid and dopaminergic pathways).

The treatment of acute intoxication with cocaine and amphetamines is generally supportive: regulation of hydration and electrolyte disturbances; treatment of hypertension, rhythm, and conduction disturbances; use of vasodilators; gastroprotection; etc. Similar to heroin, cocaine and amphetamines are known to cause severe endothelial dysfunction and hemolytic-uremic syndrome (Kavannagh et al. 2006). Therefore, antithrombotic prophylaxis should be administered.

Cocaine has several metabolites: benzoylecgonine, ecgonine methyl ester, and norcocaine. Benzoylecgonine is a potent vasoconstrictor in vitro, but does not cross the blood-brain barrier in vivo. Ecgonine methyl ester (EME) is actually a vasodilator. It is produced by metabolization of cocaine by plasma cholinesterase (also known as pseudocholinesterase, or butyrylcholinesterase). "Pseudocholinesterase deficiency" due to BCHE gene mutations, is a specific condition that could render patients more vulnerable to severe intoxication with cocaine, to prologed paralysis with succinylcholine and mivacurium.

Cocaine drug interactions could be examined in the light of three situations: cocaine intoxication, withdrawal, and long-term treatment and craving prevention. It seems there is scarce evidence of interaction between cocaine and CYP3A4 inhibitors, ketoconazole, erythromycin, and clarithromycin. There are other factors whose importance has to be established in the future, such as glutathione peroxidase-1 deficiency and microRNAs (Gallelli et al. 2017).

Cocaine intoxication leads to tachycardia, hypertension, and vasospasm. Treatment of these sometime fatal symptoms is done through the use of benzodiazepines, calcium channel blockers, and nitric oxide-mediated vasodilators. Nitroglycerine could induce reflex tachycardia through severe hypotension, so it should be used with extreme caution. Alpha-1 blockers had been tried with limited evidence. Alpha-2-adrenoceptor agonist trials had better results, especially with the

use of dexmedetomidine. There had been a widespread belief that beta-blockers could dangerously worsen hypertension during cocaine intoxication (Lange et al. 1990). However, this concept had been challenged recently. There were several Level I/II, Level III, and Level IV/V studies of β-blockers, with 1744 subjects, 7 adverse drug events, and 3 treatment failures. There were no adverse events reported for labetalol and carvedilol, mitigating hypertension and tachycardia (Richards et al. 2016). Antipsychotics have been used and studied for the treatment of hypertension and tachycardia, improving agitation and psychosis (paranoia), but there are significant risks with QTc prolongation and extrapyramidal adverse effects. Since second-generation antipsychotics have serotonergic effects, clinicians need to be aware of the potential risk of serotonin syndrome, by potentiating serotonergic effects of cocaine. Other medications include lidocaine, sodium bicarbonate, amiodarone, procainamide, propofol, intravenous lipid emulsion, and ketamine.

Cocaine withdrawal and cravings is a challenging condition due to several phenomena, including behavioral sensitization. Antipsychotics have been tried with mixed results. The biological mechanism of counteracting the effects of cocaine is thought to be due to presynaptic action on dopaminergic and serotonergic, while cocaine affects directly and indirectly the postsynaptic cascades. Data analysis shows that actually antipsychotics do not have advantages over placebo in regard to cocaine use and cocaine abstinence or craving. They could even cause more discomfort, even depression related to discontinuation (Kishi et al. 2013). Cochrane review did not support the notion of using antidepressants in the treatment of cocaine withdrawal (Pani et al. 2011). There had been some serious adverse reactions reported regarding the use of citalopram and cocaine – potentiation of serotoninergic vasoconstriction (Medicines and Healthcare products Regulatory Agency 2016). The more successful medication interaction is the one with GABAergic medications, topiramate, although there is still not enough conclusive unequivocal evidence for its efficiency.

Drug Interactions of Cocaine and Other Substances

Antipsychotics – increased risk of antipsychotic induced acute dystonias, both in intoxication and chronic treatment. Clozapine could lead to increased cocaine plasma concentrations and reduced psychotic and pressor effects.

Mood stabilizers (carbamazepine) – plasma concentrations of norcocaine increase – higher risk of hepatotoxic and cardiotoxic effects (Tenev 2008).

Benzodiazepines – oversedation and increased risk of benzodiazepine abuse.

Disulfiram – threefold increase of plasma levels of cocaine and increased risk of cardiotoxic complications.

β-blockers – very high risk of myocardial ischemia.

Nicotine – has a synergistic effect on dopamine release in the reward areas of the brain; lowers the oxygen supply, arterial pressure, and cardiac contractility; and increases the incidence of cardiac complications arising from cocaine use.

Alcohol – ethanol-induced metabolite, cocaethylene, of cocaine is more reinforcing than cocaine and is potentially more toxic.

Amphetamine and Its Derivatives

Amphetamine and its derivatives are not present in nature and represent purely synthetic substances. Amphetamine was first synthesized in 1887 and was initially used for the treatment of nasal congestion and subsequently as stimulant, athletic performance and cognitive enhancer, aphrodisiac, and euphoria inducer.

Amphetamine and its derivatives (methamphetamine and methoxy-substituted amphetamines; 3,4-methylenedioxyamphetamine (MDA); 3,4-methylenedioxy-methamphetamine (MDMA) or ecstasy; *N*-ethyl-3,4-methylenedioxyamphetamine (MDEA); 2,5-dimethoxy-4-methylamphetamine (DOM); p-hydroxydimethoxy-4-methylamphetamine (PMA)) are purely synthetic stimulants that act by increasing the monoamine levels in the synaptic

cleft (Quinn et al. 1997; Volkow and Morales 2015). The half-life of MDMA in humans is 8–10 h.

- Inhibition of monoamine uptake (competitive inhibition of dopamine uptake)
- Increase in neurotransmitter release (facilitation of dopamine release from the vesicles and increase in dopamine transporter-mediated reverse transport of the mediator into the synaptic cleft, independently from the action potential-induced vesicular release)
- Inhibition of monoamine oxidase (MAO)

The first and the second mechanisms are mediated by binding to trace amine-associated receptor 1 (TAAR1). Ecstasy is also known to increase serotonin liberation (Rudnik and Wall 1992) and the release of oxytocin.

The molecular and physiological effects of amphetamines are similar to those of cocaine, but they are known to inhibit MAO and to have virtually no local anesthetic effect. Methamphetamine has two enantiomers with the S-(+) being five times more active.

The physiological, psychological, and toxic effects of amphetamines are similar to those of cocaine and are mediated by their sympathomimetic and serotonin-mediated effects.

The underlying mechanisms of addiction, dependence, and withdrawal in amphetamine intake are associated with changes in gene expression (transcriptional and epigenetic changes) in the mesocorticolimbic projection. The major transcription factors responsible for these alterations are ΔFosB, CREB (cAMP response element-binding protein), and nuclear factor-kappa B (Rudnik and Wall 1992). The crucial role of ΔFosB overexpression in the development of drug addiction to many substances (including alcohol, cannabinoids, cocaine and amphetamines, nicotine, opioids, dissociative anesthetics, and hallucinogens) is demonstrated by the profound effect of ΔJunD in such cases. ΔJunD is an enzyme that blocks ΔFosB overexpression, and when brought to the nucleus accumbens by a viral vector, it could reverse the behavioral changes in chronic drug abuse and addiction.

The overexpression of ΔFosB in amphetamine abuse (like in cocaine abuse) leads to marked and long-standing functional effects and changes in dopaminergic neurons, especially in the nucleus accumbens, hippocampus, amygdala, and frontal cortex with the development of addiction. This addiction pattern is due to deep receptor, mediator, and structural changes in the neurons, and currently there are no known medications to counteract addiction in such patients.

Medical strategies have been developed to treat acute intoxication – i.e., for the treatment of cardiac (tachycardia, rhythm and conduction disturbances, hypertension) and vascular (vasoconstriction, endothelial dysfunction) symptoms, hyperthermia, dehydration, dyselectrolytemia, inadequate antidiuretic hormone secretion, intracranial complications (ischemic stroke and hemorrhage), respiratory failure and acute respiratory distress syndrome, and hepatic and liver failure. The hepatic failure is known to develop due to the oxidation of mitochondrial proteins and acute microsomal toxicity, combined with ischemia (vasoconstriction plus thrombosis), and renal failure is usually due to dehydration in combination with rhabdomyolysis and/or development of hemolytic-uremic syndrome (Kavannagh et al. 2006; Moon et al. 2008).

There are acute and long-term toxicity phenomena. There are several sources of data: in vitro experiments, animal models, and in vivo observations. There are still a lot of studies to be done to unequivocally prove the specific interactions and their clinical significance.

Acute toxicity	Chronic toxicity
Euphoria, well-being, happiness, stimulation, increased energy, extroversion, feeling close to others, increased empathy, increased sociability, enhanced mood, and mild perceptual disturbances. In addition, cardiovascular-related somatic symptoms, autonomic effects (dry mouth, sweating, tremor, mydriasis	Neurotoxicity Impairment in serotonin function Neurodegeneration Phenocopying phenomenon – compromising the extensive metabolizer capability; developing low tolerance to methamphetamine after a short period of

(*continued*)

Acute toxicity	Chronic toxicity
tremor, jaw clenching, and restlessness), and moderate derealization have been observed (de la Torre et al. 2004) Hyponatremia – uncommon, associated with inappropriate antidiuretic hormone (SIADH) secretion and excessive water intake (also in polymorphic reduced COMT activity) Fulminant hepatitis and hepatic necrosis have been described too	experiencing less toxicity of the substances (EM to PM status change)

The toxic effects are related to the metabolism of MDMA and methamphetamine and their metabolites. MDMA is a substrate to CYP2D6, but also a potent inhibitor through the so-called mechanism-based inhibition, by the phenocopying phenomenon. The effective enzyme amount decreases, so even genotypically active metabolizers become similar to poor metabolizers. Regardless of the genotype/phenotype, it could take up to 10 days to resynthesize CYP2D6 and restore it back to its baseline level of activity after even a single recreational dose. It was thought that there were sex differences, with 67% of males and 100% of females having such phenotyping effect, exposing them to the adverse effects of the drugs. Female subjects in the study setting would display more intense physiological (heart rate and oral temperature) and negative effects (dizziness, sedation, depression, and psychotic symptoms).

Currently it had been proven that the wide genotype allelic variations of CYP2D6 actually do not play the role they had assigned before. That could be due to the alternate pathways during the first phase of methamphetamine and MDMA metabolism: CYP1A2, CYP2B6, CYP2C19, and CYP3A4. They also have multiple genotype/ phenotype variations and could undergo the same phenocopying phenomenon, thus making the occurence of acute and chronic adverse effects dose-independent and unpredictable.

The second phase of metabolism of MDMA is through COMT. It converts the catechol metabolites HHMA and HHA into HMMA and HMA. The same enzyme inactivates dopamine (DA) and noradrenaline (NE). It exists in two forms. MB-COMT is in the brain and S-COMT in the liver/kidneys. There are two basic functional polymorphisms – valine (val) to methionine (met) substitution at codon 108 in S-COMT and at codon 158 in MB-COMT. The latter variant, the Met allele, is associated with low enzymatic activity, while the former, val allele, has higher activity. Roughly one fourth of the population has low activity, and one fourth has high activity. The lower the activity, the higher the toxicity through the accumulation of the immediate active MDMA metabolites – HHMA and HHA. **This could subsequently increase the risk of clinical symptoms including hyperthermia, hypertension, tachycardia, seizures, serotonin syndrome, and rhabdomyolysis.**

HMMA plasma concentrations play significant role, regardless if these are linked to CYP2D6 genotype (higher with two functional alleles). Genotypes of COMT val158met or 5-HTTLPR with high functionality (val/val or l/*) determine greater cardiovascular effects and with low functionality (met/* or s/s) negative subjective effects, such as dizziness, anxiety, and sedation.

An important role is attributed to glutathione S-transferase (GST) in the detoxification of HMMA. There had been some data in vitro showing differences in toxicity related to GST polymorphism, which actually had not been observed in vivo. The conjugation during elimination process in phase II of metabolism goes through SULT system, leaving sulfate conjugated MDMA urinary metabolites and UGT system – glucuronide conjugate urinary metabolites. There are also some genetic variants, especially in UGT system, which could lead to decreased enzymatic activity, hence longer elimination and increased toxicity of MDMA (UGT2B15).

MDMA and amphetamine toxicity is dynamically related to individual differences in DAT expression both at pre- and postsynaptic levels. The dopamine transporter gene could modify indirectly the receptor signaling done by the drugs. Reduced SERT potentiates self-administration of MDMA and cocaine (Brox and Ellenbroek 2018).

Types of consequences due to interactions or enzymatic polymorphisms

1) MDMA-induced toxicity

Enzymatic polymorphism	Interactions
Phase I – CYP2D6, CYP1A2, CYP2B6, CYP2C19, CYP3A4 Phase II (COMT, GST, SULT, UGT) – Less active isoenzyme genotype, or depletion of normal activity genotype (phenocopying) NT reuptake transporters: SERT, NET, DAT NT synthesis, breakdown: TH, TPH, COMT, MAO NT receptors	CYP2D6 inhibitors SERT inhibitors – Fluoxetine, paroxetine, citalopram NET inhibitors – Duloxetine, reboxetine DAT inhibitors – Bupropion, duloxetine 5-HT2 antagonists – Ketanserin, mirtazapine α-β-adrenergic antagonists – Carvedilol Antipsychotics (Rietjens et al. 2012)

The most dangerous toxic phenomena related to MDMA and methamphetamine are as follows:

Serotonin syndrome: (1) Mental status changes, (2) autonomic hyperactivity, and (3) neuromuscular abnormalities, all with varying signs from tremor and diarrhea to delirium, neuromuscular rigidity, and life-threatening hyperthermia. Death could occur due to increased serotonin levels via MDMA-induced 5-HT release and inhibition of 5-HT degradation via MAO inhibitors (Rietjens et al. 2012). The highest risk for this syndrome is in combination with antidepressants.

Hyperthermia: MDMA-induced cutaneous vasoconstriction and metabolic heat production.

Several dangerous reactions related to CYP2D6 inhibition had been described. Ritonavir and antiretroviral drugs have had life-threatening effects described. The unpredictability of these reactions is derived from the genetic polymorphism of CYP450 and alternate pathways for Phase I of MDMA metabolism.

Pharmacodynamic interactions that could lead to MDMA tolerance and increase the recreational dose, due to lack of the desired effect (no "high," less intense sensation of euphoria) This effect could be protective against neurotoxicity, exerted directly by MDMA or its toxic metabolites. Two mechanisms for that had been suggested. The first is the reduced 5-HT release and SSRI exerted prevention of MDMA to interact with SERT, blocking the efflux of serotonin through SERT. The second seems to be direct inhibition of CYP2D6 by such antidepressants like paroxetine and fluoxetine. Thus, MDMA metabolism is blocked. Concentration of toxic metabolites HHMA and HMA and their reactive quinones remains low. The risk of this type of interaction is that consumer could increase the dose.

Drug Interactions

It is important to clarify the timeline for assessing and predicting the drug interactions, since there is a differentiated response to MDMA and methamphetamine after infrequent one dose or seldom binges vs chronic daily use. It is possible that one and the same medication has different effect on the metabolism of these drugs after sporadic or chronic stimulation of the enzymatic activity and the genotype predisposition of CYP450, UGT, GST, COMT, and SULT. The level of affected NAT, DAT, and SERT transporters is also worth mentioning. In this context some varieties could be anticipated with regard to reaction and side effects of MDMA and methamphetamine with patients taking antidepressants, antipsychotics, or antiepileptic medications. Another very important issue is if there had been pretreatment, i.e., the person had been receiving a medication before using MDMA (or amphetamines). It could potentially change the reaction during acute intoxication, withdrawal, or maintenance of sobriety treatment. Further research needs to be conducted to elucidate individual differences (Table 2).

Of note: severe MDMA intoxication is addressed by cooling measures and use of benzodiazepines.

Antidepressants – Bupropion (CYP2D6 inhibitor) (could lower the pharmacological effects (both cardiovascular and euphoric) of methamphetamines by blocking its toxic metabolites). It had been tried in treating moderate and non-daily users. It could be administered for prolonging the abstinence period, although

Table 2

Timeline of medication intervention related to meth/MDMA use	Pretreatment	During intoxication	During withdrawal	During maintenance of abstinence
Antidepressants				
Citalopram	Prevention of depletion of 5-HT (Schmidt and Taylor 1987) (in rat models)	Could ↑ locomotor activity, through ↑ D2 receptor expression (rat models)	Could exacerbate physiologic effects	Do not improve significantly depressive symptoms
Paroxetine Fluoxetine (FLX)	Inhibition of CYP2D6, low level of active, toxic metabolites	Limited data FLX reduces 5HT depletion, does not affect hyperthermia SSRIs could ↑ risk of serotonin syndrome Not suitable to start treatment, since FLX needs 6–8 h to reach therapeutic plasma concentration, same time for elimination of MDMA	Reverse reward deficits during amphetamine withdrawal (Harrison et al. 2001)	Nonconclusive reports regarding prolongation of abstinence or treating depressive symptoms
Duloxetine	↑ MDMA levels, through inhibiting SERT and NET, ↓ tachycardia, ↓ hypertension, weak DAT inhibitor	Could be used, not enough data	Not enough data	No adverse effects noted
Mirtazapine	Could ↓ consumption, ↓ erratic sexual behaviors	Not enough data	Further studies need to be done	Not enough data
Bupropion	↑ MDMA levels, through CYP2D6 block, ↓ adverse effects			Could prolong abstinence
Imipramine		↑ risk of cardiovascular, GI, anticholinergic effects		↑ abstinence time
Sertraline	Should not be administered to patients with methamphetamine-related disorders, due to adverse effects on abstinence, AWMF (Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften www.awmf.org)			
Antipsychotics				
Haloperidol	Reduces hyperthermia ↓ depletion of 5-HT	Change subjective MDMA effects from a pleasurable state of well-being and euphoria to a more dysphoric state with slightly increased anxiety, i.e., *akathisia* (Rietjens et al. 2012)		
Clozapine	Reversal of MDMA-induced cutaneous vasoconstriction (Blessing et al. 2003) and inhibition of MDMA-induced Increases in metabolic heat production			

data is still not conclusive (Härtel-Petri et al. 2017b). From clinical perspective, one could make the case that increasing dopaminergic transmission could facilitate resolution of temporary depressive symptoms after "methamphetamine crash." Bupropion could also give false-positive urine drug screen for amphetamines, in 41% of cases (Casey et al. 2011).

Trazodone could yield false-positive urine drug screen for amphetamines, especially after pretreatment with phenothiazines.

Mood stabilizers – Lithium (dehydration more pronounced).

Antipsychotics – Quetiapine and risperidone for the treatment of depressive and psychotic symptoms in the chronic methamphetamine use syndrome. In acute phase antipsychotics and methamphetamine could reduce the efficacy of each other.

Antiretroviral drugs – Ritonavir (severe CYP2D6 inhibitor, increased level of MDMA).

α-β-adrenergic receptor antagonists – Carvedilol (could potentially decrease hyperthermia).

Alcohol – Slows down the effects of MDMA and increases nephrotoxicity, leading to high risk of lethal dehydration.

Urinary alkalinizers' (OTC medications) use leads to increased tubular reabsorption, via the increased amounts of non-ionized amphetamine. Thus, methamphetamine could have its' half-life increased two-to-three-fold, while MDMA's half-life could increase by two-fold.

Antihypertensive medications – MDMA and methamphetamine counteract their effects and could render the hypertension control more difficult to maintain in the long term.

Tobacco/nicotine – Smoking methamphetamine in combination with tobacco creates the pyrolysis product cyanomethylmethamphetamine. This metabolite has some stimulant properties (Dean 2006).

Methamphetamine-related, post-acute persistent or comorbid syndromes such as methamphetamine-associated psychosis (MAP), depressive syndromes, anxiety, and sleep disorders are usually treated in a symptom-oriented manner. The interactions could be unpredictable, could happen on many different levels, and could change dynamically. This makes it very important to use medications with the most available data for efficacy possible. Further research is warranted (Härtel-Petri et al. 2017a). Methamphetamine and MDMA could lower the seizure threshold.

Marijuana and Synthetic Cannabinoids

Cannabis is the most widely used illicit substance all over the world (Sharma et al. 2012). It has been used for centuries for recreational purposes. It contains more than 400 active substances, 61 of which are cannabinoids and have certain psychoactive properties. The main psychoactive substance is delta-9-tetrahydrocannabinol (THC). In the human body, THC binds to specific psychoactive and functional effects outside the CNS. It is used for recreational purposes, but because of its wide spectrum of effects and tendency to cause dependency and profound behavioral changes, THC is illegal in the most part of the world.

THC is derived from the leaves, stems, and seeds of the Indian hemp (*Cannabis sativa*). The parts of the plant can be smoked or taken orally, even mixed with food and cooked. When smoked, *Cannabis sativa* leaves, stems, and seeds liberate more than 2000 substances, most of which are produced via pyrolysis (Sharma et al. 2012), but the major psychoactive substance is THC. In the human body, cannabinoids bind to specific cannabinoid receptors (CB1 and CB2) that have physiological ligands (anandamides) that belong to the arachidonate derivatives. The latter act via affecting cAMP intracellular levels and ion transport (calcium and potassium) in different organs.

The multiple physiological effects of cannabinoids are mediated by two types of receptors – CB1 and CB2. CB1 are expressed mainly in the brain areas responsible for the cognitive, memory, pain, reward and anxiety, and endocrine and motor functions, while CB2 are expressed by the peripheral tissues and organs. The exact mechanisms of action of cannabinoid in the body are not

well understood, but it is assumed that the binding to cannabinoid receptors leads to the activation of several signal pathways, including dopamine, serotonin, and norepinephrinergic, GABAergic, opioid, cholinergic, glucocorticosteroid, and prostaglandin systems (Sharma et al. 2012). It is also known that cannabinoids can directly interact with opioid and benzodiazepine receptors and can affect protein, nucleic acid, and prostaglandin synthesis (Sharma et al. 2012), hormone secretion, and DNA repair and replication (Sharma et al. 2012; Reece and Hulse 2016; Li and Lin 1998; Reece 2009). CB2 receptors are expressed in multiple tissues and organs, including the gastrointestinal tract, endocrine glands, and immune systems, and this can at least partially explain the effects of cannabinoids on these structures. Moreover, there is evidence that cannabinoids interact with vanilloid and vanilloid-like receptors (Pertwee 2005) on glutamatergic and alpha-adrenergic receptors and on multiple peripheral tissues.

Cannabinoids, both natural and synthetic, have certain adverse effects on the mental status (including triggering overt psychoses), respiratory tract (including the development of obstructive lung disease and lung cancer), cardiovascular system (changes in blood pressure, ischemic organ damage, inflammatory angiitis, arrhythmias, worsening of the metabolic profile, etc.), bone loss, fetal retardation, etc. (Reece 2009).

Of special interest is the mutagenic, teratogenic, and genotoxic effect of cannabinoids that has become even more visible due to the widespread abuse of cannabis. Of crucial importance are the permanent genetic changes arising during in utero exposure to cannabinoids, leading to the formation of inheritable malignancies, such as childhood neuroblastoma, leukemia, and rhabdomyosarcoma (Reece 2009). These effects are mediated by at least three major mechanisms (Reece 2009):

- Oxidation of DNA plus inhibition of DNA repair (via induction of the formation of nitrogen-centered species and by uncoupling of mitochondrial oxidative phosphorylation), with deoxidation of guanosine to oxo-guanosine being a normal part of the endocannabinoid signaling
- Changes in enzyme activity: stimulation of MAP kinase pathway (an important factor for the induction of non-lymphoblastic leukemia), inhibition of topoisomerase II pathway, and RAD-1 inhibition and damage
- Changes in telomeres due to the inhibition of telomerase (this enzyme is present in stem cells, gonadal/germ cells, and cancer cells but not in the normal somatic cells)

In cell cultures, marijuana smoke condensates have been shown to increase the formation of reactive oxygen species (ROS) and to inhibit the synthesis of the transcription factor p53 that acts as a tumor-suppressor protein (Kim et al. 2012).

The synthetic cannabinoids (fake weed, spice, K2, etc.) are synthetic cannabinoid derivatives with stronger affinity toward the cannabinoid receptors with more pronounced psychomodulating and adverse effects and unknown safety. Their peripheral, long-term, and genetic effects are unknown and hard to predict.

The multiple receptor targets of cannabinoids, their epigenetic and genetic effects, and the unclear mechanism of signaling changes, in combination with their widespread abuse, make the treatment of cannabinoid addiction extremely difficult.

THC and CBD are metabolized mainly in the liver by cytochrome P450 isoenzymes (mainly CYP2Cs and CYP3A4). In vitro studies indicate that THC and CBD both inhibit CYP1A1, CYP1A2, and CYP 1B1 enzymes, and recent studies have indicated that CBD is also a potent inhibitor of CYP2C19 and CYP3A4. Both cannabinoids may interact with other medications metabolized by the same pathway or by inducers/inhibitors of the isoenzymes.

It is important to distinguish different pathways of metabolism, related to different ways of administering both substances. Preparations which have Δ9-THC inhibit CYP2C9 and CYP3A4. CBD inhibits mostly CYP2C19 and CYP3A4. Marijuana inhalation (pyrolysis) inducts CYP1A1 and CYP1A2. Patients with

lower activity of CYP2C9 and/or CYP3A4 (phenotypical or by genotype) could have increased plasma concentrations of other substances they take together with Δ9-THC, while CBD exposure in patients with diminished CYP2C19 and/or CYP3A4 function could lead to unpredictable risk of adverse effects of medication substrates of these enzymes. There are very few documented interactions that are proven in vitro and in vivo, such as TCAs or anticholinergic drugs that can produce significant tachycardia. This may be due to beta-adrenergic effects of cannabis coupled with the anticholinergic effect of tricyclic antidepressants. Most of the other interactions are actually hypothesized, and there is still lack of sufficient controlled trials to state evidence-based approach. Nevertheless, it could be very well expected to have increased plasma concentrations with these substrates, due to the occurrence of possible drug interactions.

	CYP3A4 substrates	CYP2C9 substrates
Δ9-THC preparation	*Antidepressants*: amitriptyline, citalopram, clomipramine, fluoxetine, imipramine, mirtazapine, paroxetine, sertraline, trazodone, venlafaxine *Antipsychotics*: pimozide, quetiapine, risperidone, ziprasidone, aripiprazole, chlorpromazine, clozapine, haloperidol, perphenazine *Benzodiazepines*: clonazepam, diazepam, nitrazepam, alprazolam, midazolam *Sedatives*: zaleplon, zolpidem *Analgesics*: buprenorphine, codeine, fentanyl, hydrocodone, tramadol, lidocaine. *Antiarrhythmics*: amiodarone *Ca channel blockers*: amlodipine, diltiazem, nimodipine, verapamil *Beta-blockers*: metoprolol, carvedilol *Protease inhibitors*: ritonavir, lopinavir, nelfinavir, indinavir *NNRTIs*: efavirenz *Antiepileptics*: carbamazepine, ethosuximide, valproic acid, zonisamide *Statins*: atorvastatin, simvastatin *Antibiotics*: azithromycin, clarithromycin, erythromycin *Antifungals*: ketoconazole, fluconazole, miconazol *Others*: dextromethorphan, sildenafil, tamoxifen, ondansetron, PPIs	*Antidepressants:* Fluoxetine, sertraline, amitriptyline *Selective AT1 angiotensin II receptor antagonists*: losartan, valsartan *Oral hypoglycemic*: sulfonylureas, glimepiride, glipizide, glyburide *NSAIDs Others*: phenytoin, S-warfarin, zolpidem
CBD preparations		**CYP2C19 substrates** *Antidepressants: amitriptyline, citalopram, clomipramine, fluoxetine, imipramine, sertraline, venlafaxine Barbiturates: hexobarbital, mephobarbital PPI: lansoprazole, omeprazole, pantoprazole, esomeprazole Benzodiazepines: alprazolam, diazepam, flunitrazepam Others: moclobemide, propranolol, nelfinavir*
Marijuana smoking lowers the concentration of CYP1A1, CYP 1A2 substrates, potentially	**1A1 substrates** *Compounds of tobacco smoke*: heterocyclic amines and polycyclic aromatic hydrocarbons CYP1A1 is a carcinogen-metabolizing enzyme. Its activation or inhibition could modify the cancer risk factors	**1A2 substrates** *Antidepressants*: amitriptyline, clomipramine, fluvoxamine, mirtazapine *Antipsychotics*: chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, perphenazine, thiothixene, trifluoperazine,

(*continued*)

	CYP3A4 substrates	CYP2C9 substrates
		ziprasidone *Others*: propranolol, caffeine, acetaminophen, riluzole, ropinirole, melatonin, R-warfarin, naproxen, ondansetron

Cannabis produces sedation, impairs psychomotor performance, and increases blood pressure and heart rate. Pharmacodynamic interactions with other sedatives can potentiate the central effects but can be decreased by psychostimulants. This review focuses on the interactions between cannabinoids and alcohol, other drugs of abuse, and prescription medicines.

It is important to note that the ratio between CBD and THC had changed over the years, with Δ9-THC having higher concentration now than in the past. Cannabidiol (CBD) had been used more and more in the treatment of epilepsy, including very recent promising results in the possible improvement of schizophrenia (McGuire et al. 2018).

Case reports suggest that concurrent use of cannabis with other illicit substances could lead to toxic interactions (Lindsey et al. 2012).

Benzodiazepines and Barbiturates

Benzodiazepines (BZDs) are among the most widely prescribed medications all over the world for a broad spectrum of indications, including insomnia, epilepsy, muscle spasms and contractures, alcohol withdrawal, and anxiety (Griffin et al. 2013). They are used in anesthesiology for premedication before general surgery because of their marked anxiolytic effect and the ability to cause anterograde amnesia. The use of some benzodiazepines (i.e., flunitrazepam) has been severely restricted due to their ability to induce abulia in combination with retrograde amnesia and the potential to be used for sexual assault and for "zombification."

Other point of concern is their ability to induce tolerance and dependence/addiction, the changes in their pharmacological profile with age, and the interactions with multiple medications.

The pharmacological effects of benzodiazepines (sedative, anxiolytic, muscle relaxation, antiepileptic) are mediated via modulation of GABAA receptor activity – i.e., in the central nervous system BZD represent GABAA agonists. The gamma-aminobutyric acid (GABA) is a universal inhibitory mediator in the central nervous system that decreases neuronal activity and excitability. The GABA receptors have three major types – A, B, and C – that represent chlorine channels, and BZDs bind selectively to GABAA. The latter is composed of five subunits – two alpha, two beta, and one gamma subunit. BZDs bind to the pocket created by α and γ subunits and change the space structure of the receptor that leads to increased binding of GABA and stimulation of GABA mediation; increased chlorine channel permeability, along with changes in sodium, potassium, and calcium membrane permeability; inhibition of calcium-dependent neurotransmitter release; and inhibition of adenosine neuronal uptake with unknown clinical significance (Quinn et al. 1997; DeVane 2016).

BZDs also have peripheral benzodiazepine receptors (DeVane 2016) that are unrelated to GABAA – in the peripheral nervous system, glia, immune system structures, etc. BZDs also act as mild adenosine reuptake inhibitors thought to explain, at least partially, their anticonvulsant and anxiolytic effects.

Barbiturates bind to a different part of the same receptor as BDZ bind. Barbiturates cause similar effects to the ones that BDZ have (DeVane 2016). While BZDs increase the frequency of the chlorine channel opening, barbiturates increase the duration of the opened state. This leads to increased risk of toxicity of barbiturates. Moreover, barbiturates are known to bind and affect other CNS and peripheral receptors, including inhibition of ionotropic glutamate receptors (kainate and AMPA receptors) and inhibition of P/Q type of voltage-dependent calcium channels

(leading eventually to inhibition of glutamate release). Barbiturates also bind to ligand-gated ionic channels (cationic – nAChR, 5-HT3 receptor, and glycine receptor ionic channels), causing depression of the CNS. The stated extra-GABAA receptor and ionic channel effects of barbiturates leading to more pronounced CNS depression compared to BZDs plus the lack of specific antagonist have led to significant restriction of barbiturate use in the clinical practice (DeVane 2016).

Benzodiazepines

BZDs were first introduced to the clinical practice in the 1960s as tranquilizers and sedatives and subsequently were administered as anticonvulsants and hypnotics.

Depending on the duration of action, BZDs are classified as having short, intermediate, and long duration of action. Short and intermediate acting are used mainly for the treatment of insomnia and long acting for anxiety. There are two main mechanisms of tolerance and addiction in BZDs (Quinn et al. 1997): downregulation of GABAA receptors in the limbic system and increased sensitivity of the benzodiazepine-GABAA receptor complex to inverse agonists. Moreover, similar to alcohol addiction and withdrawal, mechanisms have been described, including, respectively, changes in the expression of corticotropin-releasing hormone (CRF) and CRF receptor sensitivity and neuropeptide Y and increased NMDA and AMPA receptor sensitivity (affecting glutamate neurotransmission). BZD withdrawal syndrome is characterized by sleep disturbance, irritability, anxiety to panic attacks, confusion, nausea, weight loss, changes in blood pressure and heart rate, muscle stiffness, irritability, headache, perceptual changes, psychotic reactions including hallucinations and delusions, and suicidal thoughts and attempts.

In the elderly, BZDs tend to have more unfavorable profile of side effects and are therefore included in the Beers List of inappropriate medications in the elderly.

Specific adverse effects of BZDs on the central nervous system that are even more pronounced in elderly are (Griffin et al. 2013; DeVane 2016):

- Cognitive impairment and other toxic effects on the CNS, including sedation, drowsiness, inattentiveness, motor impairment, anterograde amnesia, and ataxia.
- High risk for development of tolerance and addiction with severe withdrawal symptoms in abrupt cessation.
- Anterograde amnesia, especially concerning the long-term memory and impaired implicit and explicit memory; these effects are particularly dangerous because of the possibility for drug-facilitated sexual abuse, especially in flunitrazepam intake.
- Accumulation and subsequent disinhibition with impaired perception of inherent risk of inappropriate behavior (reckless driving, sexual behavior, etc.).
- BZD-induced delirium states, especially in the elderly and/or hypoxic patients with parenchymal organ failure.

BZDs have significant drug interactions with many prescription, nonprescription, and illicit drugs, including benzodiazepines, opioids, alcohol, and over-the-counter sleep medications. Benzodiazepines are metabolized through the liver, mainly through CYP450 to CYP3A4 isoenzyme.

On the other hand, BZDs have antagonist, flumazenil, used for the acute treatment of overdose, along with the supportive treatment (infusions, antibradycardic, antihypotensive medications, diuretics, etc.).

The treatment of BZD addiction is difficult, as dependence (both psychological and physical) develops relatively quickly and includes flumazenil and cognitive behavioral therapy.

Drug Interactions

Benzodiazepines could have their plasma levels increased through the inhibition of CYP3A4. Potent inhibitors, such as fluoxetine, imipramine, erythromycin, clarithromycin, etc., increased the plasma levels of benzodiazepines through the

inhibition of CYP3A4 by the antidepressants. They could have their plasma concentration lowered (or half-life shortened) when interacting with enzymatic stimulants such as carbamazepine. Benzodiazepines could have synergistic increased depressing effect on CNS and respiratory suppression with mirtazapine, alcohol, barbiturates, and antihistaminic medications.

Barbiturates

Barbiturates were first discovered in 1864, but their widespread use in the clinical practice as hypnotics began in the beginning of the twentieth century. Because of their marked side effects and the risk of dependence and addiction, currently barbiturates are used mainly as hypnotics, anticonvulsants, sedatives, and general anesthetics (sodium thiopental) and for the treatment of severe withdrawal symptoms of alcohol and illicit drug abuse (as sedatives, like BZDs) (DeVane 2016).

Their profile of addiction and withdrawal is similar to benzodiazepines, but they have no known receptor antagonist. Therefore, the intoxication and dependence are more difficult to manage compared to BZDs, having in mind the broader spectrum of receptor and mediator systems affected by barbiturates.

Hallucinogens (LSD, Mescaline, Magic Mushrooms, Ayahuasca, Psilocybin, Dimethyltryptamine, DMT)

The classical hallucinogens are natural substances or their derivatives that cause perceptual alterations of real stimuli, described by the patients as hallucinations, via stimulation of serotonin mediation. These "hallucinations" actually represent distortion of the reality due to changes in perception. Classical hallucinogens have been used for religious and recreational purposes for hundreds of years. Classical hallucinogens are taken orally in the form of "magic drinks or potions," tablets, etc., and are rarely smoked. All act via activation of 5-HT2A receptor pathways. Depending on their chemical structure, classical hallucinogens can be divided into three major groups (Baumeister et al. 2014):

- Tryptamines: psilocin (the psychoactive compound of psilocybin, found in the magic mushrooms) and DMT (*N*,*N*-dimethyltryptamine, the psychoactive compound of ayahuasca) and its derivatives
- Lysergamides: LSD (lysergic acid diethylamide) and LSP (lysergic acid 3-pentylamide) and its derivatives
- Phenylamines: mescaline (the psychoactive compound of the peyote cactus) and DOI (2,5-dimethoxy-4-iodoamphetamine) and their derivatives

Psilocybin, dimethyltryptamine, and mescaline occur in nature, and the rest are synthetic. Ketamine, MDMA, and salvinorin A are able to induce similar changes in the state of consciousness but are not classified as classical hallucinogens because their effects are mediated via other receptor pathways.

All three types of classical hallucinogens act via the stimulation of 5-HT2A receptors (Baumeister et al. 2014) and cause distortion of environmental stimuli (i.e., temporary distortion of reality), perceived as hallucinations, traveling to or contact with other worlds, etc. They also bind to metabotropic serotonin receptors and affect large number of intracellular signaling pathways, the significance of which is not clear (Baumeister et al. 2014). These substances also tend to have antidepressant effects.

The pharmacodynamic studies on these substances have shown that they act via the stimulation of 5-HT2A receptors and can therefore cause cross-tolerance (i.e., between psilocybin and LSD). 5-HT2A antagonists (ketanserin and risperidone) can block their action. Classical hallucinogens cause rapid downregulation of the stated receptors and the subsequent development of tolerance.

The activation of serotonin receptors initiates several signal transduction pathways: G q/11 signaling route activating phospholipase C,

decreasing the activity of protein kinase C and increasing the release of calcium ion from the cells. Classical hallucinogens are also known to stimulate phospholipase A2 (with formation of arachidonate) independently of the described pathways. These substances are known to change gene expression in the brain: induction of c-fos (LSD and derivatives), egr-1 and egr-2 (LSD), etc. Hallucinogens affect the Gi/o proteins with subsequent activation of Src. They also affect metabotropic receptors (e.g., glutamate receptor mGluR2) and lead to metabolic and behavioral effect changes. It has been suggested that their hallucinogenic effects are mediated by the co-activation of 5-HT2A and mGluR2, as well as Gi/o proteins and their cascades.

5-HT2A receptors are located in several brain areas: pyramidal neurons of layer V projecting into layer I of the cortex and the thalamus (reticular nucleus, regulating the signal processing from the thalamus to the cortex). The reticular nucleus sends inhibitory GABAergic projections to the thalamus and allows the transfer of more sensory stimuli to the cortex. Psilocybin is known to decrease the metabolic activity in the thalamus, and this could be the mechanism of sensory alterations in its abuse. Probably the changes in information transfer via the stimulation of 5-HT2A receptor pathways represent the mechanism for the development of sensory hallucinations (literally opening doors of perception, described by Huxley in 1954). Classical hallucinogens have different receptor affinities and different half-lives, the longest having LSD up to 12 h).

The physiology of addiction to these substances is associated with persistent activation of 5-HT2A receptors (Baumeister et al. 2014) with epigenetic modifications leading to changes in information transfer and channeling and the need for repetitive stimuli to maintain the same level of information transfer. Medical strategies that counteract these changes are 5-HT2A receptor antagonists, such as ketanserin and risperidone. Still, some of the effects of hallucinogens, including the changes in information channeling, tend to persist in time and cause flashbacks months later, even years after the cessation of drug abuse.

Dissociative Anesthetics (Nitrous Oxide, Ketamine, Dextromethorphan, Phencyclidine, *Salvia divinorum*)

Dissociative drugs are hallucinogenic substances that alter the perceptions and the connection with the environment. They generate the feeling of detachment from the reality and from self.

The classic dissociative drugs have also anesthetic properties, and some of them are currently used in anesthesiology (both in humans and in animals). The following substances are classified as dissociative anesthetics: nitrous oxide, phencyclidine (PCP), ketamine, dextromethorphan (DXM), and *Salvia divinorum*.

Three main mechanisms of action of dissociative anesthetics have been described (Jevtovic-Todorovic et al. 1998; Sleigh et al. 2014; Anis et al. 1983; Capasso et al. 2006):

- Disruption of glutamate-mediated neurotransmission of signals via antagonizing *N*-methyl-D-aspartate (NMDA) receptors – nitrous oxide, phencyclidine, ketamine, dextromethorphan.
- Activation of kappa-opioid receptors: *Salvia divinorum.*
- Interaction with other receptors – e.g., phencyclidine inhibits nicotine acetylcholine (nACh) receptors and directly interacts with endorphin and enkephalin receptors and sigma2 receptors; phencyclidine and ketamine are partial dopamine D2-receptor agonists; and nitrous oxide blocks beta-2-subunit containing nACh channels; inhibits kainite, GABAc, AMPA, and 5HT-3 receptors; potentiates GABAa and glycine receptors; and activates two-pore-domain potassium channels.

The inhibition of NMDA receptors is known to have three effects: dissociative, neuroprotective (via inhibition of glutamatergic stimulation of neurons, which is beneficial in ischemic brain injury), and neurotoxic (inhibition of GABA and cholinergic stimulation that could cause neuronal damage) (Jevtovic-Todorovic et al. 1998). These effects are age-dependent (Jevtovic-Todorovic et al. 1998).

The first dissociative anesthetic synthetized was the nitrous oxide – discovered in 1772 by Joseph Priestley and later used as "laughing gas." Subsequently, its anesthetic purposes were discovered, and it became clear that besides its anesthetic properties, it can be administered as recreational and neuroprotective agent with risk of neurotoxicity (Jevtovic-Todorovic et al. 1998).

Subsequently, ketamine and phencyclidine were discovered and were introduced as general anesthetics. Dextromethorphan was synthetized as an opioid analogue cough-suppressing agent and is currently part of many over-the-counter syrups against cough, in combination with antihistamines, paracetamol, and decongestants. *Salvia divinorum* is a plant abundant in Mexico and South America, traditionally used for religious purposes (for divination) and gastrointestinal motility problems [Capasso]. Its major psychoactive substance, a structurally unique trans-neoclerodane diterpenoids, is known as salvinorin A. It represents a potent kappa-opioid receptor agonist. Moreover, it inhibits enteral cholinergic transmission (explaining its anti-diarrheic effect) and has some mu-opioid receptor agonist action (Capasso et al. 2006).

Dissociative anesthetics can be administered via inhalation (nitrous oxide) and ingestion, intravenously (ketamine, phencyclidine, dextromethorphan), or chewing of the leaves (*Salvia divinorum*). A major problem of ketamine is that the dry substance has no taste, odor, nor color and if added to a drink may cause dissociative state that can be used for sexual assault and kidnapping.

As it was mentioned above, the classic dissociative anesthetics (PCP, ketamine, and DXM) act mainly via antagonizing NMDA receptors, i.e., inhibition of glutamate-mediated neurotransmission. This mediator transfers the excitatory signal to the adjacent cells, and as it is one of the major players in cognition and nociception, the inhibition of its signal pathways leads to changes in cognitive functions and inhibition of pain sensation. Moreover, the inhibition of glutamate transmission may lead to disruption of vital functions, changes in the mood, sensation of detachment from the environment and from self, depersonalization, derealization, etc. One should not forget that PCP and ketamine affect dopaminergic transmission, i.e., the "reward pathway."

As a parallel with classical hallucinogens, the exact mechanisms of receptor and postreceptor action of dissociative drugs are not well understood, but currently it is assumed that these substances act via temporary blocking of the communications between neurotransmitter systems in the brain and in the spinal cord and causing disorganization of the information channeling that regulates perception (including nociception), vital functions (regulation of sleep, hunger, body temperature, muscle control, sexual behavior), mood, and cognition. In time, due to the phenomenon of neuroplasticity, permanent changes in these information channeling systems may develop, resulting in permanent changes in mood, sleep, hunger, motion, etc.

Moreover, the combined intake of dissociative anesthetics with other addictive and psychoactive substances can be extremely dangerous, due to their strong effects on vital and mental functions. The concomitant intake with antidepressant drugs can cause serotonin syndrome with lethal consequences. In combination with stimulants, dissociative anesthetics can increase the heart rate and the blood pressure to life-threatening levels. In combination with sedatives and alcohol, they can suppress breathing.

In anesthesiology the medication with nitrous oxide and ketamine is accompanied by oxygen supplementation because without oxygen these substances can decrease oxygen saturation, especially the inhalation of pure nitric oxide. The latter also leads to depletion of vitamin B12 stored and subsequent development of megaloblastic anemia and peripheral neuron damage.

DMX is taken largely in the form of cough syrup where it is combined with other substances, such as antihistamines, paracetamol, and decongestants. Extremely large quantities of cough syrup are needed to achieve hallucinations with DMX, and these contain high quantities of antihistamines, paracetamol, and decongestants that could be toxic for both the body and the brain, causing inhibition of vital functions, hepatotoxicity, rhythm and conduction disturbances of the heart, etc. Approximately 5–10% of the

Caucasian population have genetic polymorphism affecting DMX metabolism that leads to increased risk of overdose.

The treatment of addiction and withdrawal to dissociative anesthetics is very difficult, because multiple receptor systems are engaged and frequently changes in vital functions, cognition, and behavior have already developed. Because their mechanism of action involves loss of GABAergic inhibition of the cholinergic excitatory mediation, GABA agonists and cholinolytic medications have beneficial effect in such cases.

Alcohol

The ethylic alcohol (spiritus vini) is the most frequently abused mood-changing substance in the world. It affects the life of millions of people worldwide causing alcohol-related diseases. Every year approximately two million people die of alcohol-related conditions, including cirrhosis, cancer, alcohol dependence syndrome, and traumatism (Quinn et al. 1997). Alcohol has been known to mankind since the dawn of human history. Some cultures and beliefs even have their gods of happiness in alcohol-containing beverages.

From pharmacodynamic point of view, the effects of alcohol are not mediated by any specific receptor systems but rather are triggered by changes in membrane fluidity, disruption of ion channels, and changes in phospholipase and protein kinase C activity (similar to that in LSD use, but much less severe). The alcohol is known to stimulate glutamate-mediated transmission in the central nervous system via *N*-methyl-D-aspartate (NMDA) receptor activation. This effect is thought to be responsible for its sedative and amnesic effects, and the overstimulation of this receptor can cause neuronal death. The latter mechanism is probably the underlying process of development of organic brain syndrome in chronic alcohol abuse. Alcohol is known to stimulate GABAA receptors. Moreover, chronic alcohol consumption leads to alterations in GABAA benzodiazepine receptor, and probably the withdrawal symptoms of alcohol (especially anxiety and seizures) are related to these changes. Alcohol consumption changes norepinephrine levels due to persistent inhibition of alpha2-adrenergic receptors in chronic abuse and leads to dopamine release and subsequent depletion of the nucleus accumbens. Therefore, withdrawal symptoms may be, at least partially, related to norepinephrine over-reactivity and dopamine release and depletion. In favor of this hypothesis is the beneficial effect of alpha2-adrenergic blockers, dopamine and serotonin antagonists, in alcohol withdrawal syndrome (Quinn et al. 1997).

Alcohol is also known to increase the release of 5-HT from central and from peripheral nerve endings and to interact with the opioid receptors in the prefrontal cortex and cause euphoria (Quinn et al. 1997). The administration of opioid receptor antagonists, such as naltrexone, is known to suppress alcohol dependence.

The risk of alcoholism is determined by certain environmental factors, by its interaction with multiple receptor systems (including adrenergic, dopamine, serotonin, NMDA, glutamate, and opioid receptor systems), and by genetic polymorphisms of alcohol and aldehyde dehydrogenase (Quinn et al. 1997; Higuchi et al. 1995).

The alcohol withdrawal syndrome is managed with sedatives, including benzodiazepines, beta-adrenergic blockers, dopamine and 5-HT antagonists, and naltrexone, used to counteract the described receptor and signaling pathways. Alcohol dependence is very difficult to manage because this substance is widely available and easy to access. Several strategies have been applied, including sedative and disulfiram intake and behavioral therapy (Quinn et al. 1997).

To exert its desired effect, a drug generally must travel through the bloodstream to its site of action, where it produces some change in an organ or tissue. The drug's effects then diminish as it is processed (metabolized) by enzymes and eliminated from the body. Alcohol behaves similarly, traveling through the bloodstream, acting upon the brain to cause intoxication, and finally being metabolized and eliminated, principally by the liver. The extent to which an administered dose of a drug reaches its site of action may be termed

its availability. Alcohol can influence the effectiveness of a drug by altering its availability.

Alcohol has three main pathways of metabolism:

1. *Alcohol dehydrogenase (ADH)* metabolizes alcohol to acetaldehyde. It is a toxic compound. It is also a proven carcinogen, with its high activity.
2. *Aldehyde dehydrogenase (ALDH)* turns acetaldehyde into acetate, which is less active and not a carcinogen. Acetate ends up being turned into water and carbon dioxide.

   Genotype of ADH, such as ADH1B*2, is more active. It increases the levels of alcohol-derived acetaldehyde quickly and with high intensity. It is common in people of Chinese, Japanese, and Korean descent but rare in people of European and African descent. This could be a protective factor, considering that intoxication leads to unpleasant experience and possibly would lower the risk for repetitive use (and developing of addiction). ALDH1A1*2 and ALDH1A1*3 on the other hand are the most frequently formed enzymes in patients with alcohol use disorder from African-American descent. There are many environmental factors (food, stress levels, other genetic influences) that shape the alcohol metabolism in different populations. This perhaps could explain the equal distribution of alcoholism and alcohol use disorders among Caucasians, Asians, Native Americans, and African-Americans per recent observations.

   Acetaldehyde alters glial cells' function. It has psychiatric and behavioral repercussions. Normal amounts could have euphoria-inducing, anxiety-reducing, hypnotic, and memory-inhibiting effects. With higher plasma levels, aggression could occur. Acetaldehyde could also lower the preference of alcohol, i.e., aversion to voluntary ethanol consumption. This is the key concept in the use of disulfiram. The disulfiram reaction occurs when alcohol is consumed in the presence of disulfiram, which blocks irreversibly aldehyde dehydrogenase, thus increasing steadily the levels of acetaldehyde. The latter's side effects are flushing, headaches, tachycardia, arrhythmia, nausea, vomiting, and hypotension. Disulfiram also inhibits CYP2E1 too, thus increasing the plasma levels of warfarin, phenytoin, and theophylline and also decreasing the clearance of benzodiazepines such as diazepam, oxazepam, and chlordiazepoxide and also caffeine and tricyclic antidepressants such as desipramine and imipramine. Disulfiram has two toxic metabolites: diethyldithiocarbamate (DDC) and its metabolite carbon disulfide (CS2). DDC blocks the activity of dopamine beta-hydroxylase, through copper chelation. With higher levels of DDD, dopamine can no longer turn into norepinephrine. Presinaptyc norepinephrine gets depleted. Dopamine accumulation leads to secondary cardiac abnormalities.
3. *Alcohol could be also metabolized through P450 2E1 (CYP2E1)* and catalase. These enzymes break down alcohol to acetaldehyde. CYP2E1 "switches on" after large amounts of alcohol, that is, after the ADH and ALDH capacities are overwhelmed. Catalase also contributes to alcohol metabolism only at a very small extent (Edenberg 2007). CYP2E1 accounts for roughly 7% of all CYP450 isoenzymes. It is located on chromosome 10q26.3. There are three key polymorphisms in CYP2E1 gene studied as of recently. CYP2E*5 on 5′-regulatory region has two variants, G1293C (PstI) and C1053T (RsaI). CYP2E*6 is the third variant, which is detected by Dra I, one of the restriction enzymes used to digest complete genomes and pulsed field gel electrophoresis. This variant has lower activity and could lead to potentially toxic levels of acetaminphen, ethanol and styrene (Haufroid V et al, 2002; McGraw 2014). There is different data regarding its ethnic distibution. Per Mittal et al (2015) it's distributed as follows: Caucasians 9 %, African-americans 9 % and Japanese 35 %; while CYP2E1*6 seems to have been found in 19.6 % in Asians, 10.1 % in Africans, 7.7 % in Caucasians (Gurusamy and Shewade 2014).

4. *Fatty acid interactions, forming fatty acid ethyl esters (FAEEs),* which damage the liver and pancreas (Vonlaufen et al. 2007).

Drug Interactions

The alcohol-related types of drug interactions have three main dimensions: temporal, enzyme specific, and pharmacodynamic. They could be very complex and difficult to predict at times:

1. Temporal
   - Acute intoxication, especially after prolonged period of sobriety and low concentration and grade for enzyme synthesis – potential for inhibition of drugs' metabolism, through competing interaction with the same enzymes. Exposure to acute alcohol intoxication while on any of the antibiotics such as furazolidone, griseofulvin, and metronidazole can lead to disulfiram-like reaction – headaches, nausea, vomiting, and possibly convulsions. Some tricyclic antidepressants could become toxic after acute ingestion of alcohol. Warfarin could increase its plasma concentration leading to problematic bleeding. Gastrointestinal bleeding could happen with combination of non-opioid pain medications, aspirin, and alcohol, since aspirin increases the availability of alcohol.
   - Chronic use leads to a decrease in the drugs' availability, diminishing their effects, even in the absence of alcohol, for weeks after cessation of drinking. The clinical importance of this is marked as the need for increasing the dose of certain medications, which patient with chronic alcohol abuse had been taking before entering early remission from alcohol. The doses of these medications required by nondrinkers might be way lower. Chronic alcohol use could decrease the availability of rifampin. To the same token, the dose of propofol required to induce anesthesia might be increased in patients with chronic alcohol abuse. There is also increased risk of liver damage by the anesthetic gases enflurane and halothane. Chronic use of alcohol lowers the dose of antiepileptic medications, due to the stimulation of the same enzymes responsible for their metabolism, thus increasing the risk of seizures, even during sobriety periods. Propranolol could have its plasma concentration reduced, thus increasing the risk of hypertensive crisis. Acetaminophen could be transformed into toxic metabolites.
2. Enzyme-specific reactions

   Chronic alcohol use could influence carcinogenesis by several mechanisms. Acetaldehyde is a carcinogen, binding to DNA. It could form active substances, such as malondialdehyde adduct, which mediate lipid peroxidation and nucleic acid oxidation. Inducing CYP2E1 pathway also contributes to forming acetaldehyde and radicals and enhances degradation of retinoic acid affecting signaling pathways, such as estrogen signaling, favoring proliferation and malignant transformation of precancerous cells. Chronic ethanol intake is also associated with the failure of immune surveillance of tumor cells (Ratina and Mandrekar 2017). CYP2E1 catalyzes the metabolism of procarcinogens such as *N*-nitrosamines, aniline, vinyl chloride, benzene, styrene, and urethane. There is consistency in different sets of epidemiological data showing a dose-response correlation between chronic alcohol consumption and increase in the risk for breast cancer (Baan et al. 2007; Schwab 2011). The full impact of chronic alcohol use on cancer is yet to be elucidated fully. CYP2E1 is involved in the metabolism of drugs such as acetaminophen, isoniazid, chlorzoxazone and fluorinated anesthetics, hormones, and xenobiotic toxins (Schmidt and Taylor 1987).
3. Pharmacodynamic interactions

   Alcohol can potentiate the sedative effect of opioids (morphine, codeine, meperidine), tricyclic antidepressants, antihistamine medications, antipsychotics, benzodiazepines and hypnotics. Specific alcohol drinks such as beer and wine could lead to hypertensive crises

even in moderate amounts, if combined with monoamine oxidase inhibitors, especially if taken also with foods containing tyramine (cheese, some processed meat) or specific alcohol drinks such as beer and wine with monoamine oxidase inhibitors that could lead to hypertensive crises, even in moderate amounts. Dizziness and risk of falls could be exacerbated during acute intoxication with alcohol for someone taking antihypertensive medications such as nitroglycerin, hydrazaline, or with medications for Parkinsons' disease, such as methyldopa, a Parkinson's disease medication.

Nicotine

Tobacco has toxic effects on virtually all organs in the human body. These effects are generally caused by substances other than nicotine, but still, this is the major addictive substance in tobacco smoke. Nicotine is a tertiary amine, found in the tobacco plant. Both (S)- and (R)-nicotine bind stereoselectively to nicotinic cholinergic receptors (nAChRs) with the (S)-type being a more potent aAChR agonist. When nicotine enters the body (with the cigarette smoke, when dried tobacco is sniffed or when tobacco leaves are chewed), it quickly enters the bloodstream and reaches two major sites where it exerts its physiological effects – the brain and the adrenal gland.

In the brain, the stimulation of CNS nAChRs leads to activation of dopaminergic transmission (also within the "reward circle" – midbrain – nucleus accumbens and further activation of parts of the limbic system, including cortical areas). The activation of nAChRs leads to activation of other receptor pathways, including acetylcholine, norepinephrine, serotonin, GABA, glutamate, and endorphins (Benowitz 2009). In tobacco smoking, dopamine release in the brain is facilitated by nicotine-mediated augmentation of glutamate release and by inhibition of GABA release (Benowitz 2009). Moreover, in chronic tobacco smoking, inhibition of monoamine oxidase (MAO) A and B is observed, which is associated with further increase of dopamine and norepinephrine in the synaptic cleft. Therefore the two major pathways of nictoine addiction are: 1) the increae in dopamine and norepinephrine in the CNS (the nAChR - mediated stimulation of the brain reward function); and 2) activation of the limbic system are the two major pathways of nicotine addiction.

The second binding site of nicotine are the ganglion-type nAChRs in the chromaffin cells within the adrenal medulla with further epinephrine release leading to increased pulse rate, blood pressure, and contrainsular effects (Benowitz 2009).

The pharmacological interventions in nicotine addiction are directed against stopping the tobacco smoking, generally because of the undesired effects of other smoke ingredients. It consists generally of nicotine replacement – via transdermal patches, etc., and nicotine-blocking treatment (Quinn et al. 1997).

Bath Salts (Synthetic Cathinones)

Synthetic cathinones are phenylalkylamine derivatives chemically similar to the natural monoamine alkaloid cathinone (benzylethanamine, β-keto amphetamine) derived from the plant khat (*Catha edulis*). These substances were first synthesized approximately a century ago but became popular as recreational drugs in the first decade of the twenty-first century. The commonly abused synthetic cathinones (called "bk-amphetamines" for their beta-ketone moiety) resemble amphetamine in their chemical structure and mode of action (including binding to the monoamine transporters and monoamine release, reuptake and signaling within the brain, modulation of serotonin action).

The natural alkaloid cathinone is (*S*)-2-amino-1-phenyl-1-propanone – a beta-ketone amphetamine analogue. It is found in the fresh leaves of the khat plant. Khat leaves are popular for recreational purposes in the Middle East, particularly in Yemen. The intake of cathinone has sympathomimetic effect, close to that of amphetamine – euphoria, alertness, and increase in pulse rate

and blood pressure. Well-known synthetic cathinones are mephedrone, methedrone, methylenedioxypyrovalerone, methylone, butylone, dimethylcathinone, ethcathinone, ethylone, fluoromethcathinone, and pyrovalerone.

The first cathinone derivate – methcathinone – was synthesized in 1928, and 1 year later mephedrone was synthesized. The only synthetic cathinone currently approved for medical purposes is bupropion. Methcathinone was used for the treatment of depression in the 1930s–1940s and was administered for recreational purposes until the late 1990s. The administration of pyrovalerone for chronic fatigue and obesity has been investigated, but due to abuse and dependency, the drug was withdrawn.

In the beginning of the twenty-first century, there was a renaissance of synthetic cathinones as recreational drugs, initially in the UK and subsequently in the USA. These substances have been often referred to as "designer drugs" and have been sold under the name of "bath salts." The commonly sold bath salts in Europe usually contain mephedrone, and in the USA methylenedioxypyrovalerone, along with the different derivatives of pipradrol and pyrovalerone.

The main routes of administration of synthetic cathinones are nasal insufflations (snorting) or oral ingestion, but rectal, gingival, and inhalation delivery and intramuscular and intravenous injection have also been described. Moreover, synthetic cathinones are often administered in combination with other recreational substances, with or without alcohol. Their psychoactive effect appears 10–15 min after the intake and is expected to last for ½–4 h, depending on the route of administration.

As it was mentioned above, all synthetic cathinones are phenylalkylamine derivatives with bk-moiety that resemble amphetamines, so they can modulate the levels and action of biogenic amines (stimulant, sympathomimetic effects) and serotonin (effects on the mood and appetite, psychoactive effects) in the brain. Cathinones have higher polarity compared to amphetamines, and therefore they have lower penetration through the blood-brain barrier. Their pharmacodynamic and pharmacokinetic properties in humans are not well understood, and the majority of pharmacological data are derived from animal models and in vitro studies. Their effect is known to be due to increased synaptic concentration of dopamine, norepinephrine, and serotonin in the synaptic space via two major mechanisms:

- Inhibition of the monoamine uptake transporters with subsequent inhibition of the synaptic clearance of monoamines
- Release of the neurotransmitters from intracellular depots through the alteration of vesicular pH and concomitant inhibition of the vesicular monoamine transport VMAT2 receptor, responsible for the monoamine reuptake in the vesicles

From a neurobiological point of view, the main factor for the self-administration behavior, abuse, and addiction is the mesolimbic dopamine transmission (Baumann et al. 2014). The mechanisms of action of the following synthetic cathinones have been elucidated, at least in animal models (Baumann et al. 2014; Prosser and Nelson 2012):

- Methylone: inhibition of norepinephrine and dopamine via the suppression of monoamine uptake transporters (equally potent to that of methamphetamine and MDMA), inhibition of VMAT2 receptor (less potent than methamphetamine and MDMA), competitive for norepinephrine uptake and non-competitive for serotonin and dopamine), and reverse transport of neurotransmitters from the nerve terminal to the synapse (analogous to that in methamphetamine intake)
- Mephedrone: the same mechanisms of action, but less potent in increasing serotonin brain levels and faster returning of mediator levels to the baseline compared to MDMA and amphetamine
- Pyrovalerone: inhibition of norepinephrine and dopamine and little effect on serotonin reuptake with the S-enantiomer of pyrovalerone possessing higher biological activity

Based on their similarity to amphetamines, the effects of synthetic cathinones resemble much to the effects of amphetamine derivatives. The most important adverse effects of their intake are related to their sympathomimetic and serotoninergic effects: palpitations; increased blood pressure due to vasospasm; epistaxis; abdominal pain; severe rhabdomyolysis due to vasoconstriction with dehydration due to decreased sensation of thirst and increased physical activity (i.e., dancing); mydriasis with vision abnormalities; increased activity of the central nervous system with agitation, aggression, paranoia, and delusions; tremor; seizures; tachypnea; dyspnea; diaphoresis; and fever. Cases of hyponatremia in bath salt intake have been reported that are thought to be related to overhydration (as in amphetamine/MDMA users who voluntarily increase the intake of fluids because of the risk of dehydration) plus changes in antidiuretic hormone secretion [Prosser]. Cases of acute renal failure have been described that are thought to be due to rhabdomyolysis, dehydration, and severe vasoconstriction. Liver failure in cathinone users is thought to be associated with vasoconstriction, thrombosis, and concomitant use of other hepatotoxic substances. It is unknown whether cathinones have direct hepatotoxic effect, like MDMA, mediated by direct mitochondrial toxicity with oxidative modification of mitochondrial proteins (Moon et al. 2008).

Synthetic cathinones are often consumed with alcohol. Studies show that the concomitant intake of mephedrone and alcohol in rodents leads to enhancement of the psychostimulant effect via additional increase in synaptic dopamine levels (A.Cuidad-Roberts et al., 2015). This alcohol-induced potentiation of the effect of cathione can be blocked by haloperidol, but not by ketanserin.

Concerning the addiction and withdrawal, there has been no systematic research on these processes in cathinone-abusing humans. Observational studies have shown that synthetic cathinones are addictive (Prosser and Nelson 2012), with addiction/dependence symptoms and social dysfunction. Abusers report craving to repeat or increase the dose of mephedrone. Although no physical effect has been reported so far. Severe psychological dependennce may be present, inlcuding depression, anxiety, craving for continuous use, even without any reported physical effects (Prosser, Nelson JS, Nelson LS 2012). As cathinones are analogues of amphetamines, one could expect the development of marked and long-lasting changes in brain sympathies and serotoninergic receptor systems.

The treatment of acute cathinone intoxication is generally supportive – hydration and correction of electrolyte disturbances; stimulation of diuresis; increase of gastrointestinal clearance; oral administration of absorptive agents, adrenergic antagonists (beta-blockers), sedatives (benzodiazepines as in amphetamine and cocaine intoxication to counteract monoamine release and reuptake inhibition), and anticonvulsants; treatment of hyperpyrexia; treatment of rhabdomyolysis (saline infusions, intravenous loop diuretics, urine alkalization, mannitol infusions, corticosteroids, dialysis); gastroprotection; antithrombotic prophylaxis; etc.

Pharmacodynamic Interactions Between Addictive Substances

As all addictive drugs follow the same neurotransmitter pathways and the neuromediator systems tend to interact closely with each other and with endocrine signaling, the addictive drugs tend to show significant pharmacodynamic interactions that can have detrimental consequences for the body and the brain. These interactions are of importance for the treatment of drug addiction and withdrawal because of the need to decrease anxiety and CNS overexcitement via decrease in receptor sensitivity and/or inhibition of other receptor systems of the same neurons, affected by the addictive substance.

The pharmacodynamic interactions between different psychoactive medications can be explained by four major phenomena: effect on the same receptor systems, presence of both types of receptors on the same neuron, presence of the two types of specific receptors on contacting/adjacent neurons that interact, and, last but not least, interaction on subcellular and

intracellular levels (i.e., action on the same second messenger or enzyme systems within the cell) (Quinn et al. 1997).

Shown below are some examples of pharmacodynamic interactions between psychoactive substances.

Opioids are known to increase the sedative effects of benzodiazepines, and vice versa. Moreover, naloxone decreases this effect. This could be explained by at least one of the following three phenomena (Quinn et al. 1997):

- Presence of both GABAA (for benzodiazepines) and opioid receptors on the same neurons
- Presence of GABAA and opioid receptors on adjacent but related neurons
- Pharmacodynamic synergism due to changes in intracellular mediators and second messengers – in this case changes in cAMP levels and/or GABAA receptor phosphorylation via cAMP-dependent process

The sedative effects of BZDs have been shown to be diminished by naloxone, probably by downstreaming of GABAA receptors (Quinn et al. 1997).

The sedative effects of GABAA pathway-mediated substances (opioids and benzodiazepines) are also increased by alcohol. Acute alcohol ingestion also potentiates GABAA. Antidepressants, antihistamines, and anticonvulsants that interact with GABAA mediation also show additive synergism with opioids, benzodiazepines, and alcohol. Cocaine and opioids, especially heroin, also tend to interact mainly in a pharmacodynamic way (Quinn et al. 1997) – interactions between opioid and dopaminergic pathways and changes in cAMP intracellular levels.

Amphetamine and its derivatives possess MAO inhibitory properties and therefore tend to interact with MAO inhibitors in a potentially fatal way. The co-administration of both types of drugs leads to marked adrenergic activation with extreme elevation of blood pressure and pulse rate. This could result in confusion, coma and death (Quinn et al. 1997).

The combined intake of dissociative anesthetics with other addictive and psychoactive substances can also be extremely dangerous. The concomitant intake with antidepressants can cause serotonin syndrome, and in combination with stimulants, they can increase heart rate and the blood pressure. In combination with sedatives and alcohol, they can suppress breathing.

Synthetic cathinones are often consumed with alcohol, and it tends to increase their psychostimulant effect (Ciudad-Roberts et al. 2015), probably via additional increase in synaptic dopamine levels. Their effects are probably stimulated by all illicit substances that increase dopaminergic mediation.

Conclusion

The intake of psychoactive substances has followed mankind since the dawn of human history. These substances have been taken for religious and recreational purposes, as sedative or stimulant medications, and for the treatment of somatic conditions (i.e., gastrointestinal mobility disorders, for pain, etc.) and central and/or peripheral nervous system diseases and conditions. Their pharmacodynamic profiles are of crucial importance for the understanding of their pharmacological and toxic effects, addiction, possible drug interaction, and treatment of withdrawal. Pharmacodynamic drug interactions are of particular importance because of the high prevalence of multidrug abuse. The newer “designer drugs” are an emerging and potentially serious problem, because of the affection of many receptor and signaling pathways and the potential to interact with virtually all substances that affect dopaminergic mediation.

Therefore, the good understanding of the pharmacodynamic characteristics of both older and newer addictive substances will aid the diagnostic and therapeutic process in the everyday clinical practice.

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