Chapter 2

Amphetamine Usage, Misuse, and Addiction Processes: An Overview

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Abbreviations

ADHD Attention deficit hyperactivity disorder
CART Cocaine- and amphetamine-regulated transcript
MDMA 3,4-Methylenedioxymethamphetamine

INTRODUCTION

Amphetamines are synthetic drugs that share many structural and functional similarities with endogenous amines. Amphetamine (α-methylphenethylamine) is the leading compound of this class of drugs and exists in two stereoisomeric forms, of which D-amphetamine is the most potent (Taylor & Snyder, 1970). The relatively simple chemistry of amphetamines, together with the almost unlimited number of structural rearrangements that can be introduced in the amphetaminic scaffold, have led to the generation of a huge number of amphetamine derivatives (Figure 1). Some of them display a pharmacological profile which closely resembles that of the parent compound (e.g., methamphetamine), while others have atypical pharmacological properties (e.g., 3,4-methylenedioxymethylamphetamine, also known as MDMA or "ecstasy"). Nevertheless, amphetamines as a class of drug are characterized by a common mechanism of action, the possession of addictive properties, and the ability to elicit toxicity at both the central and peripheral level (Carvalho et al., 2012).

Many of the biological effects elicited by amphetamines overlap those of endogenous amines, due to the structural similarities existing between these molecules. Importantly, amphetamines do not act by directly stimulating the receptors that bind endogenous amines (mostly dopamine and norepinephrine), but rather promote the release of these molecules from neuronal terminals (Brodie, Cho, Stefano, & Gessa, 1969) (Figure 2). This mechanism of action explains why the pharmacological profile of amphetamines differs from that of drugs which directly stimulate dopamine and norepinephrine receptors, and accounts for the basis of the addictive properties of these drugs (Koob & Nestler, 1997).

USAGE, MISUSE, AND ADDICTION PROCESSES

Some of the effects elicited by amphetamines have medical relevance; therefore, amphetamine derivatives have been, and still are, used as therapeutic agents. The most common indications for amphetamines are nasal decongestion, psychostimulation, enhancement of attention, and suppression of appetite (Figure 3).

Amphetamine was introduced in the market as a nasal decongestant at the beginning of the twentieth century (Iversen, 2008), based on its ability to release norepinephrine at the level of the small vessels, causing vasoconstriction and eventually resulting in decongestion. While amphetamine proved to be very efficacious in eliciting this effect, its use as a decongestant led to wide substance misuse and abuse, and, in many cases, to cardiovascular toxicity (Iversen, 2008). Therefore, the use of amphetamines as nasal decongestants is now very limited, and narrowed to those derivatives that do not elicit psychostimulation and are devoid of abuse potential (e.g., L-methamphetamine). At variance with this, amphetamine-related drugs, and in particular D-amphetamine, are still widely used as psychostimulants in several conditions where a heightened attention is desirable, and for the reduction of appetite in the treatment of obesity.

Psychostimulation is the most well-characterized effect of amphetamine, and can be consistently reproduced at both the preclinical and clinical level. Data collected in experimental animals indicate that the psychostimulation induced by amphetamine is a complex phenomenon, which gives rise to markedly different behaviors, depending on the dose of drug administered. Low doses of amphetamine stimulate locomotor activity (Strömberg & Svensson, 1975), while higher doses trigger the so-called "stereotyped behaviors" which consist of persisting and repetitive behaviors that do not have any ethological or functional significance, such as self-grooming, gnawing, licking, or sniffing (Nelson & Ellison, 1978). A similar pattern of psychostimulation can be observed in humans, where amphetamine improves mood and attention at low doses, but triggers compulsive and psychotic-like behaviors after either the administration of high doses or prolonged

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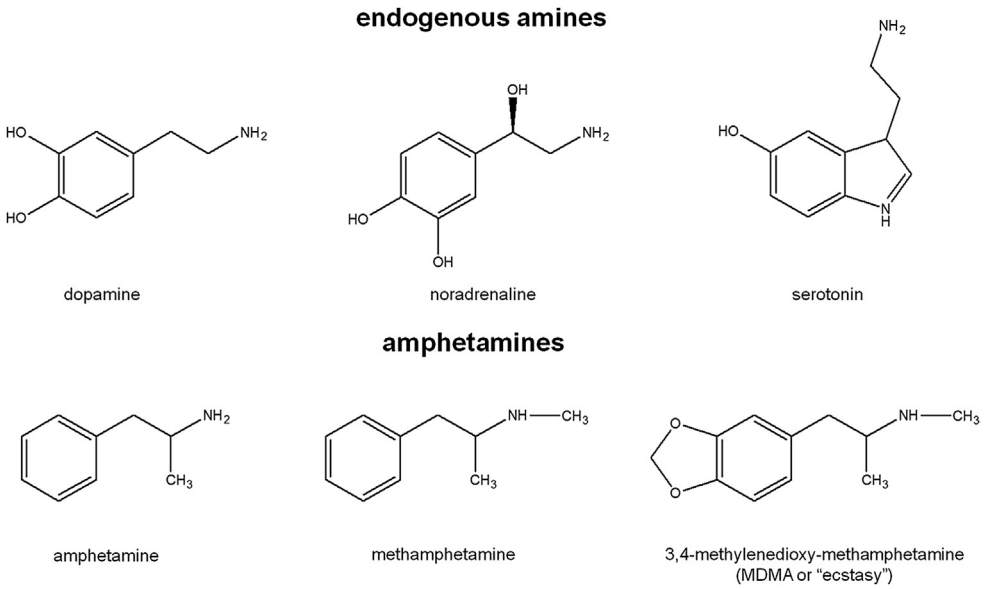

FIGURE 1 Chemical structures of endogenous monoaminergic neurotransmitters and of the most common amphetamine-related drugs. Amphetamine and methamphetamine show structural similarities with dopamine and noradrenaline, which are at the basis of the sympathomimetic effects of these psychostimulants. Conversely, MDMA displays closer structural similarities with serotonin, which justifies the peculiar pharmacological profile of this drug.

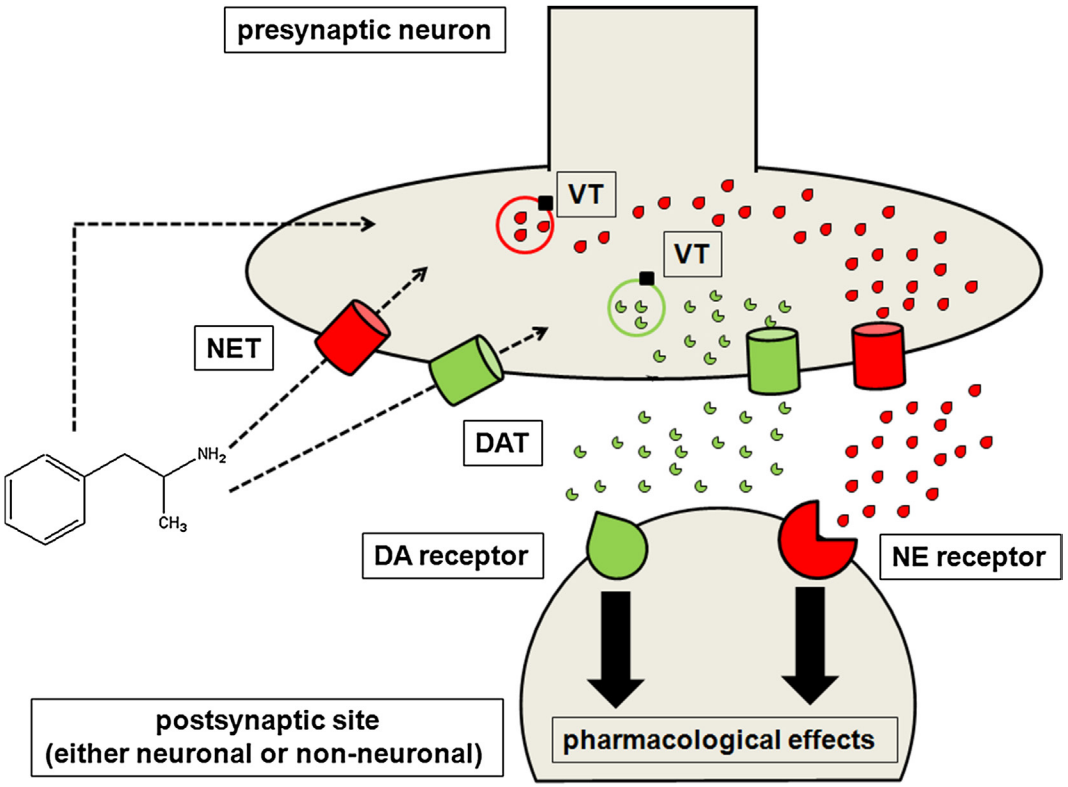

FIGURE 2 Mechanisms of action of amphetamine. Amphetamine can directly penetrate into the presynaptic terminals or, most importantly, can be taken up by the membrane transporters for dopamine (DAT) or norepinephrine (NET), according to the specific neuronal type considered. Once inside the presynaptic terminals, amphetamine is pumped inside intracellular vesicles by the vesicular transporter (VT). Thereafter, amphetamine displaces monoamines from vesicles, causing a dramatic increase in their cytoplasmic concentrations. This, in turn, promotes a massive outflow of monoamines through the membrane transporters, leading to an increase in monoamine extracellular concentrations which eventually bind to postsynaptic receptors, hence producing the pharmacological effects of amphetamine.

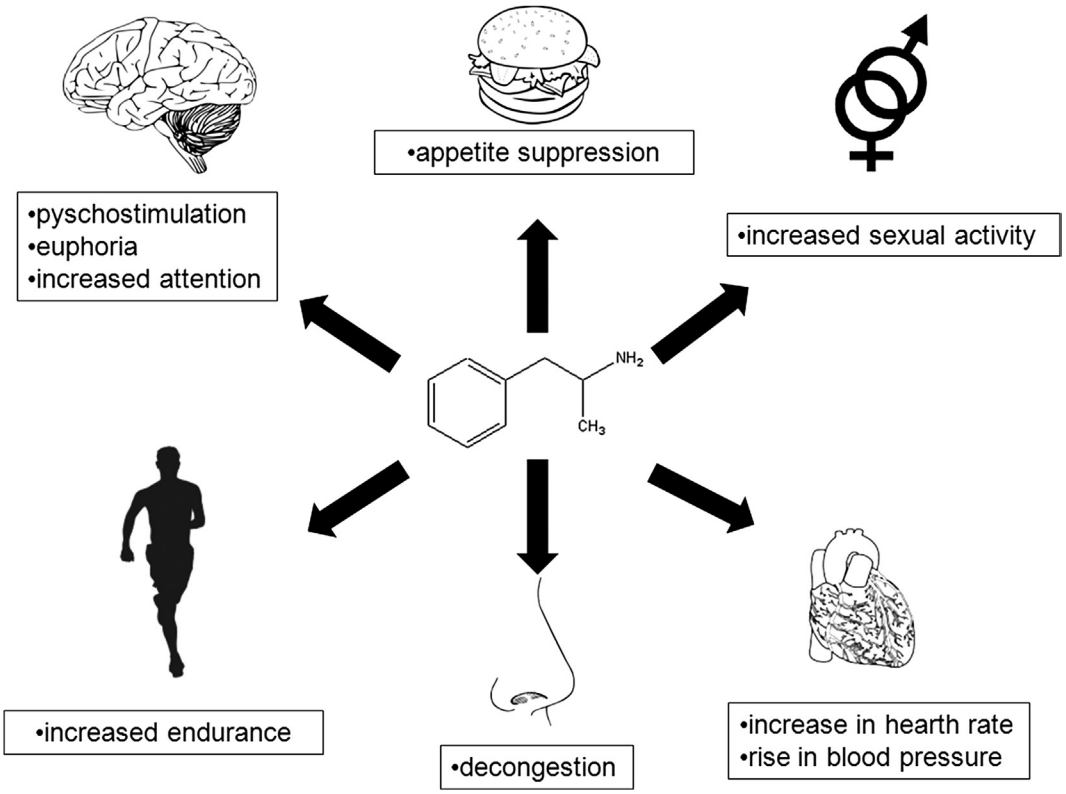

FIGURE 3 Overview of the most common effects of amphetamine in humans. Amphetamine elicits both central and peripheral effects. The majority of these effects stem from the ability of amphetamine to release catecholamines from nerve terminals. Some of the effects of amphetamine have medical relevance, while others may result in the misuse (and eventually abuse) of the drug, or toxicity.

consumption (Calello & Osterhoudt, 2004; Servan-Schreiber, Carter, Bruno, & Cohen, 1998). The psychostimulant effects of amphetamine that can be observed after its administration at low doses include euphoria, resistance to fatigue, and improved task performance, particularly of those tasks that require a sustained attention over an extended period of time (Caldwell, Caldwell, & Darlington, 2003; Servan-Schreiber et al., 1998). These effects of amphetamine appear to be of relevance not only for certain professional conditions where vigilance is crucial (e.g., the military personnel), but also for those pathologies that feature a reduction in attention, such as narcolepsy and attention deficit hyperactivity disorder (ADHD).

Today, the treatment of ADHD is the most important medical use of amphetamine. ADHD is a complex neuropsychiatric condition that becomes manifest in preschool children, and can be characterized by hyperactivity, impulsivity, and inattention, though not necessarily all at the same time (American Psychiatric Association, 2013). ADHD has an estimated world prevalence of 5–7% in children and adolescents, can severely impact the quality of life of the affected individuals, and may persist into adulthood if not adequately treated (Staller & Faraone, 2006). Even though the precise neurobiological bases of ADHD are not known, it appears increasingly clearer that this condition features a hypoactivity of the prefrontal cortex (Arnsten & Pliszka, 2011), an area critically involved in the regulation of attention and executive functions (Miller & Buschman, 2013). Therefore, the ability of amphetamine to release catecholamines in the prefrontal cortex (Shoblock, Sullivan, Maisonneuve, & Glick, 2003) may justify its effectiveness as a drug for the treatment of ADHD. Amphetamine is nowadays a drug of choice in the management of ADHD, notwithstanding the development of other effective medications, such as methylphenidate, a nonamphetaminic psychostimulant, and atomoxetine, a norepinephrine reuptake inhibitor (Reddy, 2013). Amphetamine is currently marketed under the name of Dexedrine®, which is composed of D-amphetamine, or Adderall®, which is a mixture of D- and L-amphetamine in a 3:1 ratio. Retrospective comparisons have demonstrated that Adderall has an efficacy comparable to that of methylphenidate in the treatment of ADHD (Grcevich, Rowane, Marcellino, & Sullivan-Hurst, 2001). Moreover, Adderall has a longer duration of action than methylphenidate, a feature that can significantly improve the patient's therapeutic compliance (Faraone, Biederman, & Roe, 2002). A new avenue in the use of amphetamine for the management of ADHD is represented by lisdexamfetamine, which has recently been introduced in the market. Lisdexamfetamine is a prodrug (Figure 4), that is metabolized into D-amphetamine inside the red blood cells (Pennick, 2010), and clinical studies have demonstrated that lisdexamfetamine has a positive effect on the symptoms of ADHD and can be more efficacious than methylphenidate (Soutullo et al., 2013).

The reduction of appetite is another effect of amphetamine and its related drugs that has medical relevance. Initial reports describing the potential of these substances as pharmacological aids in the treatment of obesity date back to the twentieth century

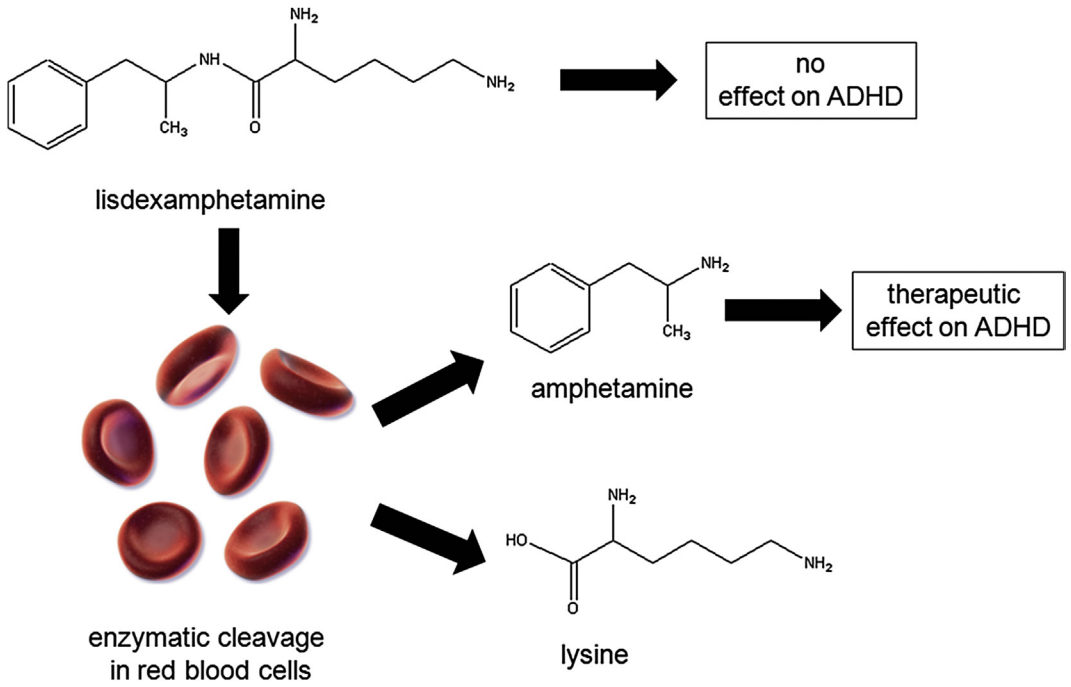

FIGURE 4 Structure and fate of lisdexamfetamine. Lisdexamfetamine is a conjugate of D-amphetamine and the amino acid L-lysine, and is converted into its constituents after enzymatic cleavage in the red blood cells. Lisdexamfetamine has emerged as a new drug in the treatment of ADHD due to its more favorable pharmacokinetics and lower abuse liability compared with amphetamine.

(Pointdexter, 1960); thereafter, several different amphetamine derivatives have been widely used for this indication (Ricca et al., 2009). Interestingly, the mechanisms underlying appetite suppression by amphetamines appear to differ from those that mediate psychostimulation. For example, fenfluramine, which has long been used as an appetite suppressant, has a preferential effect on the serotonergic system (Trifunovic & Reilly, 2006). Moreover, several studies have demonstrated that amphetamine stimulates the synthesis of the cocaine- and amphetamine-regulated transcript, an endogenous peptide which has appetite-suppressant properties (Stanley et al., 2001). The effect of amphetamines on appetite has been consistently shown to promote significant weight loss in obese patients. However, tolerance to this effect has been described together with weight regain after treatment discontinuation, which limits the efficacy of these drugs in the long term (Ricca et al., 2009). Moreover, the use of amphetamines as appetite suppressants is plagued by the emergence of severe adverse effects at the level of the cardiovascular and respiratory systems. In this regard, it is worth mentioning the epidemic of pulmonary hypertension observed in obese patients under treatment with fenfluramine (MacLean, 1999). Notwithstanding these limitations, amphetamines are still used for the treatment of obesity, due to both the constantly growing incidence of this disease in Western countries, and the shortage of alternative effective medications (Ricca et al., 2009). While some amphetamine derivatives such as fenfluramine and sibutramine have been withdrawn from the market, others such as the combination of phentermine/topiramate have been introduced for the treatment of obesity (Cosentino, Conrad, & Uwaifo, 2011).

Besides the medical use and the licit use by certain profession, for example, military personnel (Caldwell et al., 2003), amphetamine and its related drugs are widely misused as performance enhancers. Amphetamine consumed for this purpose may come from either illegal or legal sources, and major geographical and social differences in this phenomenon have been reported. Interesting examples of this are the misuse of amphetamine by athletes, truck drivers, and college students, providing a picture of the reasons why amphetamine may be misused, the factors that may underlie this practice, and the risks connected with it.

The misuse of amphetamine and other psychostimulants in sports has a long history, and dates back to the twentieth century (Avois et al., 2006). Athletes may take amphetamine due to its central effects, which may increase alertness and produce some attitudinal advantages; for example, athletes engaged in sports that are based on physical contact might want to heighten their aggressive attitude toward their opponents (Avois et al., 2006). In addition, amphetamine has been used in sports due to its peripheral effects, which may ameliorate performance by increasing cardiac output, and then elevate the amount of blood that reaches the muscles (Docherty, 2008). Even though the most recent reports by the World Antidoping Agency have documented the existence of newer substances that can be illicitly used as performance enhancers (e.g., cardiac stimulants, synthetic erythropoietin), amphetamine is still part of the array of doping substances currently used in sports (Docherty, 2008).

Truck drivers are another category of people who largely misuse amphetamine, as indicated by several surveys performed in different countries which found a prevalence of this phenomenon ranging from 0.9% to 70% (Girotto, Mesas, de Andrade, & Birolim, 2014; Gustavsen, Mørland, & Bramness, 2006). Interestingly, amphetamine misuse by truck drivers is associated with specific social and economic factors, such as young age, night driving, earning a high salary, and undertaking long trips (Girotto et al., 2014).

Thus, truck drivers are willing to take amphetamine, as its psychostimulant properties may help them to keep up with their work and, in turn, maintain a high salary.

The studies available to date consistently indicate that amphetamine misuse by athletes and truck drivers is a worldwide phenomenon (Docherty, 2008; Girotto et al., 2014). At variance with these data are those of another well-documented form of amphetamine misuse, namely that by college students, which is far more common in the USA than in other countries (Berbatis, Sunderland, & Bulsara, 2002). In this particular case, amphetamine usually comes from medical prescriptions that are diverted to nontherapeutic use, rather than from the illicit market. Therefore, the significant misuse of amphetamine by college students in the USA is due, at least in part, to the higher rates psychostimulant prescriptions for the treatment of ADHD compared with the rest of the world (Berbatis et al., 2002). Surveys carried out in various colleges across the USA have indicated that up to 30% of students engage in the illicit use amphetamine and other psychostimulants that were originally prescribed for ADHD (McCabe & West, 2013). Social factors play a role in this habit, as misuse of amphetamine was found to be more common in those students who had lower grade averages (McCabe & West, 2013). In line with this, college students consume amphetamine and other psychostimulants in the first instance because these substances are able to sustain attention and increase the number of study hours, and are envisioned as an aid to pursue a brilliant academic career (Teter, McCabe, LaGrange, Cranford, & Boyd, 2006). Nevertheless, recreational use of psychostimulants prescribed for ADHD as "party drugs" has also been observed, although the prevalence of this habit is lower than that reported for the use of the same drugs as performance enhancers (Teter et al., 2006). Different patterns of psychostimulant misuse have been observed in college students, which include either the combined consumption of methylphenidate and amphetamine or the intake of either substance alone (Teter et al., 2006). Interestingly, Teter et al. (2006) reported that college students used Adderall "… more than other prescription stimulants on their campus due to its availability and lower occurrence of ups and downs," which is likely due to the long duration of action of this drug (Faraone et al., 2002).

The misuse of amphetamine deserves particular consideration, as this practice may pose serious health risks, and can also serve as a gateway to subsequent abuse of the drug. As mentioned earlier, amphetamine acts as a sympathomimetic drug; hence, it may induce tachycardia and hypertension. Even though these effects are generally well tolerated, they may be lethal under specific conditions (Spiller, Hays, & Aleguas, 2013). For example, the sympathetic stimulation by amphetamine may promote heart failure and/or cerebral hemorrhage in people with preexisting cardiac and circulatory problems. In the case of athletes, it is noteworthy that amphetamine may amplify the effects of physical activity, and cause a further increase in both heart rhythm and sweating, which may become harmful (Docherty, 2008). Moreover, it has to be considered that the central effects of amphetamine may alter both the perception of stimuli and reaction times, often leading to an overestimation of one's capabilities and increasing the propensity to commit risky actions. This is particularly well exemplified by the higher rate of car accidents recorded among truck drivers who misuse amphetamine (Girotto et al., 2014).

An important feature of amphetamine misuse is that people who engage in this practice often ignore and/or underestimate both the immediate and long-term risks that may be associated with the use of the drug. This has been very well documented by a survey performed to ascertain the reasons college students adduce to justify their misuse of amphetamine and other psychostimulants (DeSantis & Curtis Hane, 2010). College students usually consider the misuse of amphetamine in the form of Adderall "morally acceptable," as it is done to "get better grades," and "not just to get high." Therefore, students envision this behavior as different from the intake of "party drugs," such as methamphetamine and MDMA. Moreover, Adderall is regarded as a safe substance, because "it is produced by the pharmaceutical industry," and most importantly, is "given to children." Finally, the risks related to the misuse of Adderall are often downplayed by the argument that both the effects and the legal consequences associated with this practice are somewhat milder than those that may arise from the intake of other licit and illicit substances, such as ethanol, cocaine, or marijuana (DeSantis & Curtis Hane, 2010).

In order to properly understand the significance of all these findings, it is important to mention that several studies have demonstrated how the use of amphetamine in the management of ADHD is almost completely devoid of health risks for the treated children (Merkel & Kuchibhatla, 2009). Side effects, when present, are generally of mild intensity and may be overcome by altering the drug administration regimen. Furthermore, when used according to standardized therapeutic protocols, Adderall has a negligible abuse liability (Merkel & Kuchibhatla, 2009). Notably, current evidence indicates that patients with ADHD who had received proper pharmacological treatment during their childhood showed no increase in substance abuse later in life, compared with ADHD patients who had no access to therapy (Merkel & Kuchibhatla, 2009). Taken together, these considerations may partly explain why the risks related to the misuse of amphetamine as a performance enhancer are often neglected or downplayed.

As mentioned earlier in this chapter, amphetamine elicits its pharmacological effects by stimulating the release of catecholamines from presynaptic terminals at both the central and peripheral levels. The ability to elevate dopamine concentrations in the so-called "shell" region of the nucleus accumbens, which is located in the ventral striatum, is thought to underlie the abuse properties of this drug (Di Chiara & Imperato, 1988). The release of dopamine in the shell of the nucleus accumbens is considered to be a critical mechanism that is stimulated by natural rewards, and directs the individual's behavior toward the search for further rewarding stimuli (Di Chiara et al., 2004). A crucial point to be considered in this respect is that rewarding stimuli promote a rapid, so-called "phasic," release of dopamine, which is in contrast to the slow, or "tonic," release of this neurotransmitter observed under physiological conditions (Wanat, Willuhn, Clark, & Phillips, 2009). Importantly, the phasic release of dopamine may also be attained after the administration of drugs with abuse properties, including amphetamine, and this effect is thought to be a key step in mediating the reinforcing and abuse properties of drugs (Grace, 2000). When used for medical purposes, amphetamine is usually taken either by the oral route or in the form of extended-release formulations. These ways of amphetamine administration trigger a tonic increase of dopamine levels in the brain, which is in line with the evidence that amphetamine has a negligible abuse potential when administered for medical purposes and according to standardized therapeutic protocols (Heal, Smith, Gosden, & Nutt, 2013). Furthermore, it

is important to consider that the abuse properties of a drug are also dependent on the ability of the drug to trigger rewarding effects in a narrow time window from its intake. In fact, this may promote a form of associative learning that links the intake of the drug with the onset of its pleasurable effects, and favors subsequent drug intake (Di Chiara et al., 2004). Therefore, the slow pharmacokinetics that involves oral administration of amphetamine renders the drug less desirable, compared with other routes of administration, and may justify why amphetamine is scarcely addictive when taken orally (Heal et al., 2013). Nevertheless, studies on the misuse of amphetamine as a performance enhancer have shown that a significant percentage of individuals (up to 40%) take amphetamine by nonoral routes, such as snorting and smoking (Teter et al., 2006). Importantly, amphetamine may trigger a phasic release of dopamine when taken in this way (Kirkpatrick et al., 2012). This suggests that there is a risk that misuse of amphetamine can result in overt substance abuse, at least in those cases where the drug is taken by nonoral routes.

The addictive properties of amphetamines are well acknowledged, and these drugs have been widely abused since the twentieth century (Iversen, 2008). Reports on drug abuse worldwide indicate that amphetamines are the second most commonly abused substances after cannabis (Singleton, Degenhardt, Hall, & Zabransky, 2009). Interestingly, the abuse of amphetamines is characterized by geographical differences, with a marked prevalence in the Pacific and East Asia areas, although other regions, such as the Middle East and Eastern Europe, are increasingly being interested in this phenomenon (Singleton et al., 2009). Defining the abuse of amphetamines is a complex issue, with regard to the type of drugs involved and their sources, habit prevalence, and factors that promote it. Epidemiological studies usually report the cumulative prevalence of the abuse of amphetamines and, when specific drugs are considered, the focus is often on methamphetamine and MDMA. Even though empirical evidence indicates that amphetamine is also abused, no exhaustive data exist on the prevalence of this habit. In this regard, it is, however, noteworthy that the so-called "amphetamine epidemics" have usually involved methamphetamine, and that amphetamine has been historically abused at lower rates than methamphetamine has (Iversen, 2008). These findings could be explained in light of the fact that the effects of amphetamine are somewhat different from those elicited by other commonly abused amphetamine-related drugs. For example, amphetamine does not elicit the pleasurable social effects that can be observed after the intake of MDMA, and which contribute to driving the consumption of this drug, but rather it can induce psychosis, particularly when it is taken over a long period of time (Cruickshank & Dyer, 2009). Moreover, data collected in experimental animals indicate that the effects of amphetamine do not overlap those of methamphetamine with regard to stimulation of dopamine release in specific brain regions (Figure 5). While both

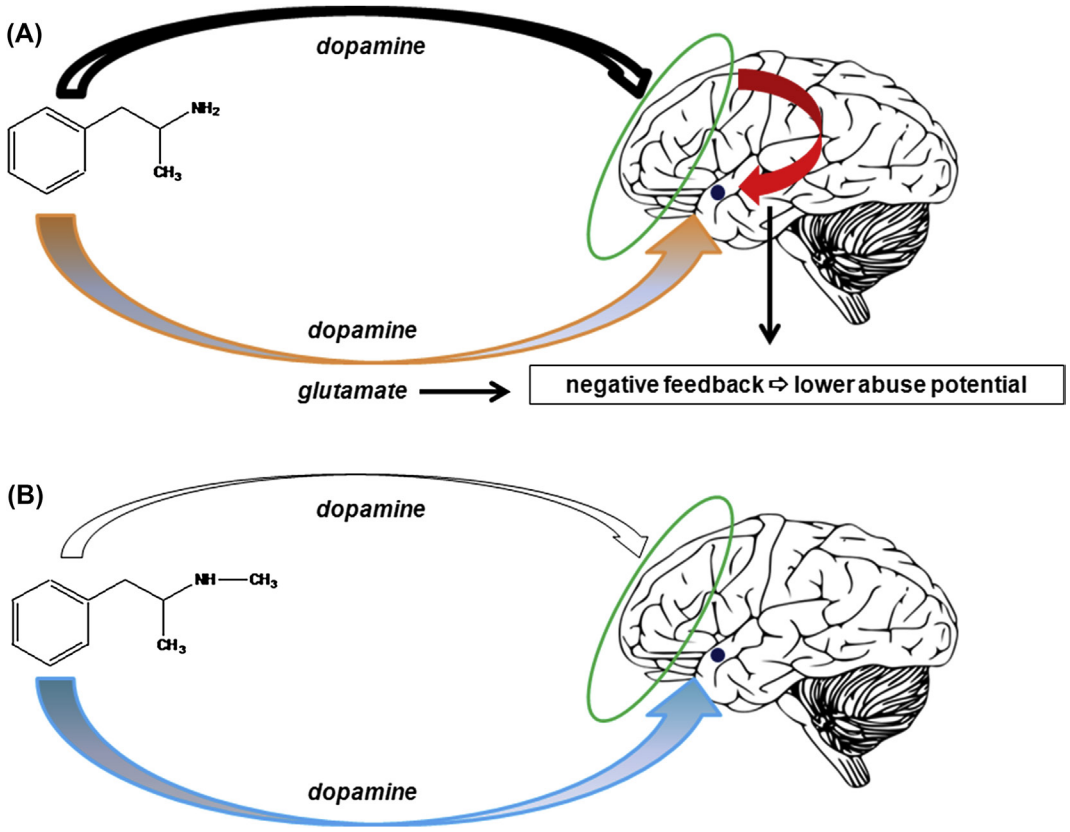

FIGURE 5 Effects of amphetamine and methamphetamine on the brain with regard to their abuse potential. Both amphetamine (A) and methamphetamine (B) stimulate dopamine release in the nucleus accumbens "shell" and the prefrontal cortex, but amphetamine elicits a stronger effect than methamphetamine in the latter brain region. Moreover, amphetamine, but not methamphetamine, elevates the levels of glutamate in the nucleus accumbens. Taken together, these effects would promote sort of a negative feedback, which would eventually self-limit the abuse properties of amphetamine (A).

these drugs elevate dopamine levels in the shell of the nucleus accumbens, amphetamine is significantly more potent than methamphetamine in stimulating dopamine release in the prefrontal cortex (Shoblock et al., 2003). It has been suggested that dopamine release in the prefrontal cortex could act to counteract the effects of heightened levels of dopamine in the nucleus accumbens (Shoblock et al., 2003). In line with this, amphetamine could be able to self-limit its rewarding effects, and this would render the drug less prone to engender an abuse habit (Iversen, 2008). It is also noteworthy that amphetamine, but not methamphetamine, promotes the release of glutamate in the nucleus accumbens (Shoblock et al., 2003), which has been suggested to inhibit the mechanisms of reward (Carlezon & Wise, 1996).

Another interesting point to take into account with regard to the abuse of amphetamine is the consumer's attitude toward the drug. People who are addicted to amphetamines and rely on the illegal market to get their drugs are more interested in those substances that are able to produce a state of "high" or "rush," which is one of the effects that drives the addiction to these substances (Iversen, 2008). Methamphetamine is by far the most potent amphetamine-related drug in eliciting these effects, which is in line with the high prevalence of its abuse. Moreover, addicts usually take amphetamines by nonoral routes, such as intravenous injection, snorting, or smoking which, as mentioned earlier, are the routes that are associated with stronger pleasurable effects of amphetamine-related drugs. As for amphetamine, it is important to remark that people who take this drug, either for medical reasons or as a performance enhancer, usually take it by the oral route (Iversen, 2008). By resulting in an attenuation of pleasurable effects (Heal et al., 2013), this may significantly contribute to reduce the likelihood of developing a real dependence toward amphetamine. Notably, this is also in line with the fact that the majority of people who take amphetamine manage to take the drug "on demand" (e.g., while studying or engaging in work) without ending up in an overt substance dependence. Currently, the diversion of amphetamine prescriptions to nonoral routes of administration is being greatly limited by the development of extended-release preparations, which makes tampering with the drug for nonmedical use more difficult. Nevertheless, the possibility that amphetamine may be taken by nonoral routes of administration exists, and has to be carefully considered, not only with regard to the threatening effects of the drug itself, but also because it may be part of a polydrug use, hence influencing the effects and addictive properties of other substances.

Applications to Other Addictions and Substance Misuse

Based on the current theories that entail a pivotal role for mesolimbic dopamine in drug addiction, the ability of amphetamine to promote dopamine release in the ventral striatum acquires particular relevance, as this effect might prime the brain to the addictive effects of other substances that are able to stimulate dopamine transmission in the same area (Figure 6). Evidence collected in experimental animals substantiates this view by showing that amphetamine can amplify the intake of cocaine and ethanol in self-administration paradigms (Potthoff, Ellison, & Nelson, 1983; Valadez & Schenk, 1994). Similar findings have been obtained in humans, where amphetamine has been demonstrated to increase both cigarette smoking and the reinforcing effects of nicotine (Cousins, Stamat, & de Wit, 2001; Tidey, O'Neill, & Higgins, 2000). It is noteworthy that some studies have demonstrated how the subjective effects of amphetamine are increased in ethanol drinkers, suggesting the risk of a comorbid consumption of these substances (Stoops, Fillmore, Poonacha, Kingery, & Rush, 2003).

At variance with these findings, studies in rodent and primate models of drug self-administration have indicated that amphetamine may actually reduce the reinforcing effects of cocaine (Chiodo & Roberts, 2009; Czoty, Gould, Martelle, & Nader, 2011). Interestingly, similar effects of amphetamine have also been reported in humans. Thus, acute pretreatment with amphetamine has been found not to increase the self-administration of the substance by individuals not dependent on the drug (Stoops, Vansickel, Lile, & Rush, 2007). Moreover, studies in psychostimulant-dependent people have shown that chronic substitution treatment with amphetamine can be useful for the management of cocaine and methamphetamine dependence (Galloway et al., 2011; Greenwald, Lundahl, & Steinmiller, 2010; Rush, Stoops, Lile, Glaser, & Hays, 2011). The latter data seem to suggest that amphetamine would not pose a risk for the development and/or exacerbation of dependence for other drugs, but would actually reduce it. However, two important points have to be considered with regard to these studies. First, experimental evaluation of the effects of amphetamine in humans is usually performed by administering the drug orally and/or by employing extended-release formulations. As mentioned earlier in this chapter, these modes of administration are characterized by slow pharmacokinetics, and are less likely to cause drug abuse than the routes of administration usually preferred by amphetamine-dependent individuals (e.g., intravenous injection, snorting). In this light, it is worth mentioning that a study has shown that D-amphetamine exerts a profile of effects similar to that of methamphetamine, when the drug is taken by the intranasal route of administration (Kirkpatrick et al., 2012). Second, the effects of amphetamine observed in individuals formerly dependent on other psychostimulants may not completely overlap those that the drug elicits in psychostimulant-naïve individuals. For example, it is feasible that amphetamine prevents relapse in methamphetamine-dependent individuals simply by attenuating withdrawal symptoms, rather than by acting on the neuronal circuits involved in methamphetamine dependence (Galloway et al., 2011). Therefore, notwithstanding these encouraging effects of amphetamine substitution therapy, it should be kept in mind that amphetamine does have abuse potential, and its improper use may end in drug dependence. Hence, the use of amphetamine has to be strictly limited to medical purposes according to precise therapeutic protocols.

Another potential risk related to the nonmedical use of amphetamine involves the neurotoxic potential of this drug, as independent preclinical studies have consistently demonstrated that amphetamine induces neurotoxicity (Fuller & Hemrick-Luecke, 1980; Jonsson & Nwanze, 1982). Remarkably, epidemiological studies have shown a higher incidence of Parkinson's disease, a neurodegenerative pathological condition, in people who abused amphetamines early in life than in the general population (Garwood, Bekele, McCulloch, & Christine, 2006), which would suggest a causal link between this drug and neurodegeneration. As of today, no exhaustive follow-up data on the neurotoxic effects

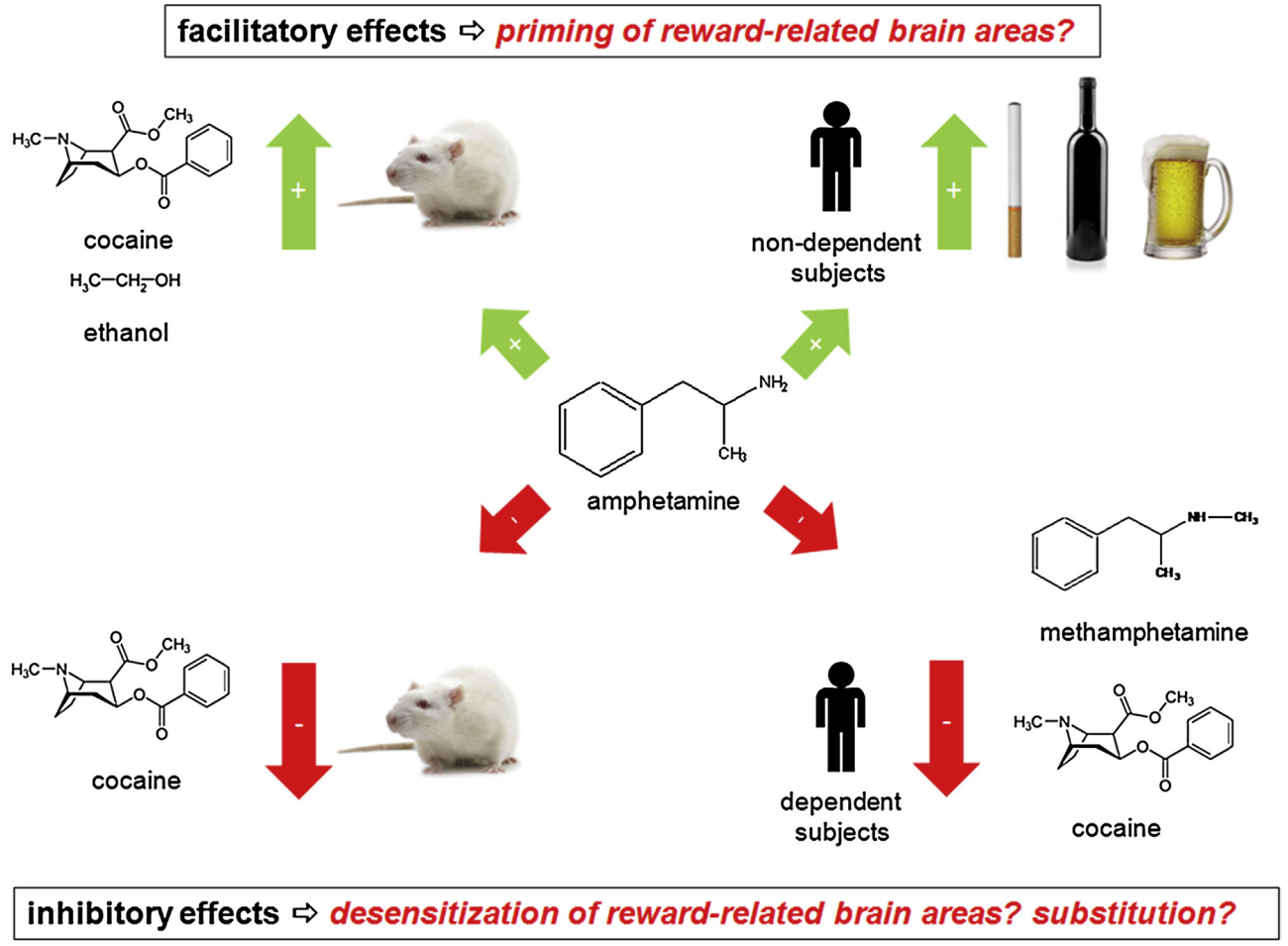

FIGURE 6 Possible influence of amphetamine on the dependence on other psychoactive drugs. Amphetamine has been demonstrated to amplify the effects of certain drugs of abuse in both experimental animals and humans. However, amphetamine has also been shown to attenuate the effects of other drugs of abuse, particularly in people dependent on other psychostimulants. These drug–drug interactions may have significant implications for the ability of amphetamine to influence the development of dependence toward other substances.

of amphetamine taken for either medical or nonmedical purposes are available. However, the neurotoxic potential of amphetamine should be considered besides its abuse potential, as it may pose a health risk, particularly in those cases when the drug is taken at high doses for recreational purposes and/or in combination with other substances that may be toxic to the brain.

DEFINITION OF TERMS

Abuse liability It is the propensity of a drug to induce dependence. Abuse liability is high for those drugs (e.g., opiates) that are highly addictive and the intake of which has a significant detrimental impact on the social and productive life of an individual.

Amphetamine epidemics It is the widespread occurrence of amphetamine-related drug abuse in specific geographical regions at a particular time.

Executive functions They are integrated functions that regulate attention, cognition, flexibility, and task solving. The prefrontal cortical regions have a crucial role in regulating these functions. Amphetamine can influence executive functions by acting on the prefrontal cortex.

Extended-release formulation It is a pharmaceutical formulation that releases a predetermined amount of a drug over a long period of time. These types of formulations are particularly suitable for long-term therapy, and to improve the patient's compliance, as use of them reduces the number of drug administrations.

Gateway hypothesis It is the theory that postulates how the preexposure to one drug may amplify the effects of either the same drug or other drugs taken at a later time.

"High" or "rush" This describes the state characterized by an intense psychostimulation often associated with altered sensorial perception and hallucinations. This state is attained when amphetamines are administered by fast delivery routes (e.g., intravenously), and is considered to be one of the causes underlying amphetamine dependence.

Nucleus accumbens "shell" It is a region of the ventral striatum that plays a crucial role in reward and gratification. The nucleus accumbens "shell" is considered to be a key region in drug dependence, as all addictive drugs share the ability to increase the extracellular dopamine levels in this region.

Party drug It is a drug that is consumed for nonmedical purposes, mainly due to its pleasurable effects. Party drugs include substances

of different pharmacological classes (e.g., psychostimulants, ethanol), and are often consumed in a social context, such as parties or raves.

Polydrug use It describes the simultaneous use of two or more psychoactive substances. Polydrug use may be observed in dependent individuals, and is often carried out to amplify the pleasurable effects of drugs.

Self-administration It is a procedure that consists of the autonomous administration of drugs by humans, or by experimental animals, according to specific schedules. The procedure in animals is used to study drug dependence at the preclinical level.

Stereotyped behavior Repetitive behavior characterized by the execution of purposeless movements. This behavior is typically observed in experimental animals treated with dopaminergic drugs, but may be also displayed by human amphetamine addicts who take the drug at high doses or for a long time.

KEY FACTS

Key Facts of ADHD

- Attention is the behavioral process that allows one to focus on specific stimuli, while ignoring others present at the same time.
- Attention is critical for the execution of a wide range of everyday tasks and for goal-oriented behaviors.
- ADHD is one of the major disorders that feature a reduced attention, though it may also be associated with symptoms such as hyperactivity and impulsivity.
- Based on the spectrum of symptoms presented, ADHD can be classified as inattentive type, hyperactive-impulsive type, and combined type (both inattentive and hyperactive).
- It is estimated that about the 5–7% of children and adolescent worldwide may suffer, or have suffered, ADHD.
- ADHD becomes evident at preschool age, and may persist in later life, if not treated.
- ADHD may have high costs for the health systems, due to the need of pharmacological treatment and supportive measures.
- A deficient dopaminergic transmission in the prefrontal cortex is thought to be one of the mechanisms that underlie ADHD.
- Amphetamine is a first choice drug in the management of ADHD, due to its ability to elevate dopamine levels in the prefrontal cortex, hence counteracting this deficit.

Key Facts of Dopamine

- Dopamine is a catecholaminergic neuromodulator present at both the central and peripheral level.
- Dopamine critically regulates important physiological functions, including attention, goal-oriented behavior, and movement.
- There are three major dopaminergic circuits in the brain: mesocortical, mesolimbic, and nigrostriatal.
- Perturbations in the brain levels of dopamine are associated with neurological and/or psychiatric diseases.
- Examples of these diseases are Parkinson's disease, caused by a hypofunction of the nigrostriatal dopaminergic circuit, and psychosis, caused by a hyperfunction of the mesolimbic dopaminergic circuit.
- Dopamine is also crucial for drug abuse, as all addictive drugs increase the levels of this neuromodulator in the nucleus accumbens "shell" region.
- Amphetamine may release dopamine from presynaptic terminals; hence, dopamine is a key player in both the peripheral and central effects of amphetamine

SUMMARY POINTS

- This chapter summarizes the main aspects of amphetamine use, misuse, and abuse.
- The medical uses of amphetamine are presented, discussing both the therapeutic and side effects of amphetamine.
- The misuse of the drug is discussed with reference to the underlying factors, and to both the social and geographical differences of this habit.
- Attention is dedicated to the misuse of amphetamine by college students, which is increasingly emerging as a major concern.
- The risks related to the misuse of amphetamine in terms of toxic effect and the development of dependence are presented, and the misconception of these risks is discussed.
- Finally, the chapter reviews the possible interactions between amphetamine and other substances of abuse, together with the risks related to the neurotoxic potential of amphetamine.

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