Stimulant Drugs and Stimulant Use Disorder

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KEYWORDS

• Stimulants • Stimulant use disorder • Attention-deficit hyperactivity disorder • Overdose • Opioid use disorder

KEY POINTS

- Stimulant medications are a specific class of drugs commonly prescribed to treat conditions, such as attention deficit-hyperactivity disorder and narcolepsy.
- Addressing the clinical complications related to stimulant use and stimulant use disorder requires a comprehensive approach that includes prevention, treatment, and harm reduction strategies.
- These strategies should be tailored to the specific needs of the individuals who are affected by stimulants and should involve a multidisciplinary team of health care providers, public health officials, and community organizations.

INTRODUCTION

Stimulant medications are a specific class of drugs commonly prescribed to treat conditions, such as attention-deficit hyperactivity disorder (ADHD) and narcolepsy.[1] These medications work by increasing the levels of certain chemicals in the brain, including dopamine and norepinephrine (NE), which help regulate attention, impulse control, and arousal.[2,3] The most commonly prescribed stimulants include methylphenidate (MPH) (eg, Ritalin) and amphetamine (AMP) compounds (eg, dextroamphetamine).[4] Currently, it is estimated that 16 million US adults and 2.8 million children use stimulants each year.[5]

Stimulants exert various effects on the body.[6] At lower dose, they could cause euphoria, whereas higher dose may lead to symptoms, such as increased heart

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Anesthesiology Clin ■ (2023) ■–■
https://doi.org/10.1016/j.anclin.2023.09.003 **anesthesiology.theclinics.com**

rate, elevated blood pressure, and enhanced cognitive function.[7,8] In addition, stimulants can suppress appetite, leading to reduced hunger and weight loss.[9] This side effect is more common at higher doses or when the medication is taken for an extended period. Stimulants can also interfere with sleep patterns, leading to difficulty falling asleep or staying asleep. It is important to monitor vital signs regularly, especially in individuals with preexisting cardiovascular conditions.

Stimulant medications can be addictive when misused.[10] Using stimulants at higher doses, more frequently, or through non-approved routes (such as snorting or injecting) can significantly increase the risk of dependence and addiction.[11] Misuse of stimulants can lead to a cycle of escalating drug use, tolerance, and withdrawal symptoms, when reducing or stopping their use.[12]

A large number of studies have focused on stimulant use among adolescents.[13] Because stimulants can impact neurodevelopment and are associated with high-risk behaviors, they can have very serious consequences in young populations.[14] Some unique patterns were reported in previous studies. For example, it was found that higher percentage of adolescent methamphetamine users were females, which is less common with other substances.[15]

There have been debates among researchers about stopping stimulant use preoperatively due to the concerns of perioperative impact of MPHs, specifically on cardiovascular stability and possible counteraction of sedatives and anesthetics.[16] Because of their potential for abuse and addiction, many stimulant medications, such as AMPs and MPH, are classified as controlled substances.[17] Currently, stimulants are tightly regulated across the nation, and their medical use is closely monitored.

Although the regulation of stimulant prescribing is strengthening, the global prevalence of stimulant use has increased yearly in the last decade.[5] There has been a significant rise in the use of AMP-type stimulants in many counties and regions.[18] Multiple studies have shown that stimulant use and stimulant use disorder are associated with a range of health and public health issues, including psychiatric and cardiovascular morbidity, infectious disease transmission, drug-associated crime, and homelessness.[19] Stimulant misuse has led to a significant increase in overdose deaths in the United States (**Fig. 1**).[20]

In the current review, the authors summarize several key points of stimulants and stimulant use disorder, including their indications, short-term and long-term adverse effects, current treatment strategies, and association with opioid medication.

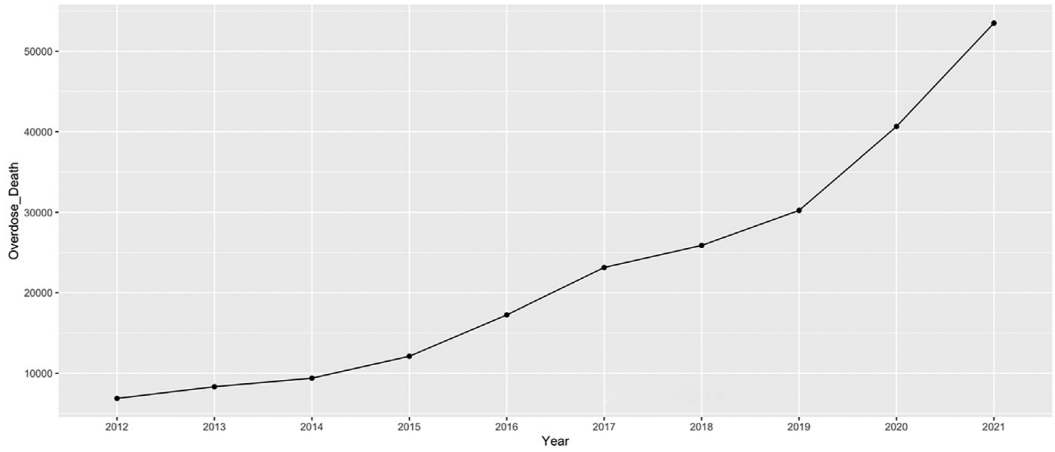

Fig. 1. National overdose deaths involving stimulants. (*Data from* National Institute of Drug Abuse.)

History of Stimulants and Their Clinical Use

In the nineteenth century, chemists began isolating and studying the active compounds within stimulant plants. In 1855, the German chemist Friedrich Gaedcke isolated and named the active ingredient in coca leaves as "cocaine."[21] This marked an important milestone in understanding the pharmacologic properties of the stimulants. In the late nineteenth and early twentieth centuries, the use of stimulant medications expanded into the medical field.[22] Cocaine, for example, was initially used as a local anesthetic due to its numbing properties.[23] However, the addictive nature of cocaine became apparent, leading to restrictions in its medical use. In the 1960s and 1970s, stimulant medications, particularly MPH (Ritalin), gained recognition as effective treatments for ADHD in children.[24] Stimulant medications continue to be the primary treatment option for ADHD today.

ADHD is a neurodevelopmental disorder that commonly begins in childhood and can persist into adulthood.[25] ADHD is characterized by a persistent pattern of inattention, hyperactivity, and impulsivity that can significantly impact an individual's functioning and daily life. The symptoms of ADHD can vary, but they generally fall into two categories, namely inattention and hyperactivity/impulsivity.[26] Inattention can manifest as a difficulty sustaining attention and staying focused on tasks or activities, being easily distracted or frequently making careless mistakes, trouble organizing tasks and activities, or exhibiting forgetfulness and frequently losing or misplacing things. Hyperactivity and impulsivity can manifest as restlessness and difficulty staying still or sitting for extended periods, excessive talking and difficulty waiting for their turn, acting without thinking of the consequences, and interrupting or intruding on others' conversations or activities. The exact cause of ADHD is not fully understood, but it is believed to result from a combination of genetic, environmental, and neurologic factors.[27]

Indications for Stimulant Use

As the most famous and commonly used stimulant, caffeine is consumed worldwide in various foods and drinks. Its moderate stimulating properties have promoted its use among athletes, students, and professionals looking for enhanced physical and cognitive performance. MPH- and AMP-related drugs share some (but not all) structural properties and are both used for medical and recreational purposes.[28]

MPH is approved for ADHD in children and adults and for narcolepsy (as a second-line treatment) in adults.[29] Its misuse as a cognitive enhancer has led to categorization of this agent as a controlled substance, as is the case for all the following stimulants. AMP-based medications are also indicated in ADHD and narcolepsy. Lisdexamfetamine is an inactive prodrug that is converted into dextroamphetamine after absorption into the bloodstream, developed with the goal of providing a longer duration of effect with less abuse potential.[30] In addition to ADHD, it is approved for binge-eating disorder. Methamphetamine, which is structurally close to AMP but retains a greater risk of abuse, is also approved for ADHD and can be tried under very strict precautions only in weight reduction programs for patients in whom alternative therapy has been ineffective.

Cocaine is Food and Drug Administration (FDA)-approved for the introduction of local anesthesia of the mucous membranes for diagnostic procedures and surgeries on or through the nasal cavities of adults. It also has an off-label use as treatment of epistaxis before cauterization or packing.[31] A systematic review in 2016 mentioned that cocaine was the most widely used topical preparation by otorhinolaryngologists for operative procedures.[32]

Mechanisms of Action

ADHD has been linked to a dysfunction in multiple neurotransmitters, but a substantial amount of research has primarily focused on the impact of dopamine and noradrenaline alterations in various brain structures.[33] For example, studies have shown that both AMP and MPH result in increased dopamine and noradrenaline availability in striatal and cortical regions but with different mechanisms. This will in turn modulate brain behaviors such as cognition and executive function, emotional responsivity, and reward processes, contributing to improvement of ADHD symptoms.[34]

Along with other direct effects of stimulant medications, MPH blocks the reuptake of two neurotransmitters, NE and dopamine, in presynaptic neurons. More specifically, it inhibits the NE transporter and dopamine transporter (DAT), increasing the concentration of these neurotransmitters in the synaptic cleft.[35]

AMPs are sympathomimetic amines with central nervous system (CNS) stimulant activity, but they are structurally distinct from catecholamines (dopamine, NE, and epinephrine).[36] Like MPH, AMPs also increase dopamine and NE availability at the synaptic level by blocking NE and dopamine reuptake into the presynaptic neuron. However, they also promote the release of catecholamines from the presynaptic nerve terminals and increase cytosolic dopamine concentrations by interacting with the vesicular monoamine transporter-2 protein, in addition to an inhibitory action on the monoamine oxidase.[37] The structurally related compound methamphetamine shares similar pharmacodynamic properties to other AMP-type stimulants but shows higher penetration into the CNS and a longer duration of action that could result in an increased risk of addiction.

Topical cocaine shares similar action to local anesthetics such as lidocaine, causing sodium channel blockade that interferes with action potential propagation.[38] This Vaughn-Williams class IC effect also increases the risk of conduction disturbance and tachyarrhythmias.[39] In addition, cocaine inhibits monoamines reuptake transporters.

Prescription Stimulants and Nonmedical Use

Prescription stimulants include AMPs, MPH, and other similar drugs. **Table 1** summarized commonly prescribed stimulants.[40] Stimulant medications can be quickly absorbed and function rapidly. The behavioral effect can occur within 30 minutes of administration, reach peak within 3 hours, and last until ~5 hours.[41]

AMPs are prescribed to treat ADHD and narcolepsy.[42] They can help increase attention, decrease impulsiveness, and control behavior in individuals with ADHD. For narcolepsy, AMPs can help reduce excessive daytime sleepiness. Nonmedical use of AMPs refers to the recreational use or abuse of the drug. This includes using AMPs without a prescription or using them in higher doses than prescribed. Nonmedical use of AMPs is illegal and can have serious health consequences.[43]

Table 1
Summary of stimulant medications

	Generic Name	Brand Name
Stimulant Medication	Amphetamine, armodafinil, atomoxetine, benzphetamine, dextroamphetamine, dexmethylphenidate, diethylpropion, lisdexamfetamine, methamphetamine, methylphenidate, modafinil, phendimetrazine, phentermine	Adzenys, Nuvigil, Strattera, Adderall, Focalin, Vnvanse, Desoxyn, Provigil, Concerta, Dexedrine, Focalin, Ritalin

Methamphetamine is chemically similar to AMP but has a more potent effect on the brain and a higher potential for abuse, with a long-lasting and more intense effect. Methamphetamine is classified as a schedule II controlled substance in the United States due to its high potential for addiction and abuse.[44] Methamphetamine can be used medically for the treatment of ADHD. It is also used for the short-term treatment of obesity in some rare case. However, due to its high potential for abuse and addiction, its medical use is tightly regulated and limited. With its lipophilic form, methamphetamine can be absorbed through oral, pulmonary, nasal, intramuscular, intravenous, rectal, and vaginal. Its onset time can range from ~5 to ~20 minutes. Nonmedical use of methamphetamine is illegal and poses serious health risks. Methamphetamine addiction is a significant concern. Continued use of methamphetamine can result in tolerance, with higher doses needed to achieve the same effect, and dependence, where the body becomes reliant on the drug to function normally.[45]

Benzphetamine is an AMP derivative.[46] It is used as a short-term adjunct to a reduced-calorie diet and exercise program in the treatment of obesity. It helps individuals with obesity to consume fewer calories and achieve weight loss. Benzphetamine can cause various side effects, including increased blood pressure, heart rate, insomnia, restlessness, dry mouth, constipation, and dizziness. Taking benzphetamine concomitantly with other diet medications can lead to the development of a rare, potentially fatal lung complication, namely pulmonary hypertension.

Cocaine acts on similar neurotransmitters as methamphetamine.[31] Cocaine can be used medically as a local anesthetic for certain surgical procedures, such as in nasal and eye surgeries. However, its medical use is limited and highly regulated. Cocaine's direct effect on the DAT can amplify its outcomes. Some studies have showed the association between cocaine and physiologic changes in the cardiovascular system via its impact on NE. Nonmedical use of cocaine is illegal and poses significant risks.[3]

Armodafinil is used to treat excessive sleepiness caused by narcolepsy or shift sleep work sleep disorder. It can enhance wakefulness by increasing the release of dopamine level. Armodafinil can also cause a series of side effects.[47] Common side effects include headache, nausea, dry mouth, nervousness, and difficulty sleeping. Serious side effects are rare but can include severe allergic reactions, chest pain, irregular heartbeat, and mood changes.

Modafinil is a non-AMP CNS stimulant. It is primarily prescribed to promote wakefulness and treat narcolepsy. It is classified as a eugeroic or wakefulness-promoting agent. Different from AMPs, modafinil shows fewer peripheral side effects at therapeutic doses. As a newly developed stimulant, it can serve as a replacement for AMP in short-term operations. Modafinil's long-term effects in large population need more study.[48]

Stimulant Use Disorder and Associated Complications

Stimulant use disorder, also known as AMP use disorder or stimulant addiction, is a recognized substance use disorder characterized by the problematic and compulsive use of stimulant drugs, such as cocaine, AMP-type substance, and other types of stimulant, which can produce similar harmful effects. It has been reported that the global prevalence of cocaine and AMP use disorder was 0.4% and 0.7%, respectively. There has been a significant increase of misuse of stimulants since 2015.[49]

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Diagnostic Criteria of Stimulant Use Disorder

Based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), stimulant use disorder is a pattern of AMP-type substance, cocaine, or other

stimulant use leading to clinically significant impairment or distress occurring within a 12-month period. DSM-5 criteria included abuse and dependence under stimulant use disorder, with various severity categories to reflect different levels of severities.[50]

Some of the criteria used to diagnose stimulant use disorder include (1) taking larger amounts or using stimulants for longer periods than intended; (2) spending a significant amount of time obtaining, using, or recovering from stimulant use; (3) cravings or a strong desire to use stimulants; (4) continued stimulant use despite experiencing social, occupational, or interpersonal problems related to its use; (5) giving up or reducing important social, occupational, or recreational activities due to stimulant use; (6) continued use of stimulants in physically hazardous situations; (7) tolerance, requiring larger amounts of stimulants to achieve the desired effects; and (8) withdrawal symptoms or using stimulants to avoid or alleviate withdrawal symptoms. The severity of stimulant use disorder can be classified as mild, moderate, or severe based on the number of criteria met.[51]

Symptoms and Complications Associated with Stimulant Use Disorder

Psychiatric and neurocognitive symptoms

The misuse or abuse of stimulants can have negative effects on mental health. Research has indicated that there may be an increased risk of certain psychiatric disorders associated with stimulant use, particularly when used recreationally or in higher doses than prescribed.[52] A range of psychiatric and neurocognitive symptoms could be caused by stimulant use, including euphoria, arousal, reduced fatigue, positive mood, increased libido, behavioral disinhibition, and short-term improvement in attention and cognition. These symptoms may be more pronounced during periods of intoxication or withdrawal from stimulant substances. With long-term use of methamphetamine, users may experience more severe symptoms. Some studies have suggested a potential link between stimulant use and the development or exacerbation of conditions, such as anxiety disorders, bipolar disorder, substance use disorders, and psychosis.[53] Methamphetamine use-associated psychotic symptoms were also referred to as methamphetamine psychosis. Studies have demonstrated that younger age and longer duration of use are associated with a higher risk of psychosis.[54] Common symptoms include hallucinations, suspiciousness, delusions, and odd speech.

For stimulant users, common symptoms of withdrawal include sleep disturbance, depression, anxiety, craving, and cognitive impairment, which were likely to be the results of the decrease in presynaptic monoamine stores and receptors, as well as methamphetamine-induced neurotoxicity. Physically, users will experience headache, chills, sweating, palpitations, angina, dry mouth, taste changes, nausea, vomiting, diarrhea, and abdominal cramping.[3]

Cardiovascular System Symptoms

Stimulants, both prescription medications and illicit substances, can have significant impacts on the cardiovascular system.[55] Stimulant use can lead to an elevation in heart rate and blood pressure. This can be particularly problematic for individuals with preexisting cardiovascular conditions, such as hypertension, coronary artery disease, and heart failure. The increase in the heart rate and the blood pressure can exert additional strain on the cardiovascular system, potentially leading to adverse events such as arrhythmias, myocardial ischemia, or cerebrovascular events. Stimulant use has been associated with the development or exacerbation of cardiac arrhythmias, including regular and irregular tachyarrhythmia and ectopic beats. In some cases, these arrhythmias can be serious and require medical intervention. Stimulants can cause vasoconstriction, which is the narrowing of blood vessels. This

constriction can reduce blood flow to vital organs, including the heart, and potentially lead to cardiovascular problems or complications. Certain stimulant substances, such as cocaine, have been linked to an increased risk of acute cardiovascular events, including heart attacks, strokes, and sudden cardiac death. These events can occur even in individuals without preexisting cardiovascular conditions.[56]

Infectious Diseases

The transmission of infectious diseases through stimulant use is a concerning public health issue, particularly in cases where stimulants are used intravenously or shared among individuals. Intravenous drug use, including the injection of stimulant drugs, poses significant risk for the transmission of blood-borne infectious diseases. Sharing needles, syringes, or other drug paraphernalia can result in the transmission of infections such as HIV (human immunodeficiency virus), hepatitis B, and hepatitis C.[57] These infections can be spread through the sharing of contaminated blood or bodily fluids.

Stimulant use can also lead to impaired judgment and risky behaviors, including engaging in unprotected sexual activity or sharing drug-related equipment.[58] These behaviors can increase the risk of acquiring or transmitting sexually transmitted infections or blood-borne infections. In addition, prolonged stimulant use, especially in high doses or with a pattern of chronic abuse, can negatively affect the immune function. This can make individuals more susceptible to various infections, including respiratory infections, skin infections, and other opportunistic infections. Stimulant use, particularly in the context of addiction or prolonged use, may be associated with poor hygiene practices, inadequate nutrition, and compromised general health. These factors can further increase the risk of infectious disease transmission.

Social Behavior/Crime Related to Stimulant Use

There is evidence to suggest a relationship between stimulant drug use and certain types of crime.[59] Stimulant drugs, such as cocaine and methamphetamine, are classified as controlled substances in many jurisdictions due to their potential for abuse and associated risks. The production, distribution, possession, or sale of these substances outside of legal frameworks can be considered criminal offenses. Consequently, individuals involved in the illicit drug trade, including users, dealers, and producers, may engage in criminal activities to obtain or distribute stimulant drugs. Although stimulant drugs can increase energy, alertness, and focus, they can also induce feelings of agitation, paranoia, and aggression, especially in high doses or with chronic use. This can potentially lead to aggressive or violent behaviors, including assault, domestic violence, or other criminal acts.

Treatment of Stimulant Use Disorder

Medication treatment

Currently, there are no FDA-approved medications for the specific treatment of stimulant use disorder.[60] Clinical trials for stimulant use disorder were conducted, but generally with small sample size, inconsistency design and outcome definition, making it difficult to obtain conclusions applicable in the clinical practice.[61] For example, some trials used urine drug screens as outcome indicator of stimulant use disorder, which is an indirect estimation of pharmacotherapy treatment effects.[62]

Currently available medications for treatment of stimulant use disorder in the clinical practice, such as MPH, naltrexone, bupropion, mirtazapine, and modafinil, are targeting neurotransmitter pathways, including dopamine, serotonin, g-aminobutyric acid, glutamate, and opioid. An alternative strategy is to reduce cravings for stimulants,

with medications such as dextroamphetamine, rivastigmine, bupropion, nicotine, and naltrexone.

For acute treatment, benzodiazepine or an antipsychotic agent can be used for methamphetamine toxicity. Haloperidol can be applied for pediatric population. For stimulant-associated blood pressure change, antihypertensive medication can be considered.

Cognitive Behavioral Therapy

Simulant users generally experience multiple behavioral issues. Interventions to target sex or age-related behaviors have showed to be beneficial for stimulant users, especially for younger populations. Interventions can target antisocial activities, risky sex practices, depression, and drug use. In adolescent users, risky sex and depression have showed to be among the most important treatment targets. Stress management was also considered to be a useful treatment.[61]

Treatment for stimulant use disorder typically involves a combination of behavioral therapies, medications (in some cases), and support systems. Behavioral therapies such as cognitive behavioral therapy and contingency management can help individuals address underlying issues, develop coping skills, and modify maladaptive behaviors associated with stimulant use. Support groups such as 12-step programs Narcotics Anonymous can also provide valuable peer support. In some cases, medication-assisted treatment may be used to aid in the recovery process. Medications such as bupropion, naltrexone, or certain antidepressants have shown some efficacy in reducing cravings and promoting abstinence from stimulants, although research on medication treatments for stimulant use disorder is still developing.[61]

Stimulant Regulation Guidelines

In the United States, there are multilevel and multi-aspect regulations for stimulant medications, which are primarily overseen by the Drug Enforcement Administration and the FDA.[63] The regulation of stimulants typically involves the several key components.

1. Classification: Stimulants are usually categorized into different schedules or classes based on their potential for abuse and medical use. The classification determines the level of control, prescribing regulations, and penalties for unauthorized possession or distribution. The scheduling system varies between countries, but it often ranges from schedule I (highest level of control) to schedule V (lowest level of control). Based on Controlled Substances Act, a federal law that classifies drugs into different schedules based on their potential for abuse and medical use, most stimulants, such as AMPs (eg, Adderall) and MPH (eg, Ritalin), is classified as schedule II substances indicating that they have a high potential for abuse and may lead to severe psychological or physical dependence.[64]
2. Prescription requirements: Stimulants classified as schedule II substances require a written or electronic prescription from a licensed health care professional, such as a physician or psychiatrist. The prescription must be issued for a legitimate medical purpose, and the health care professional must adhere to specific prescribing guidelines and regulations. This requirement helps ensure that stimulants are used appropriately under medical supervision. Health care professionals need to assess patients and prescribe stimulants based on their clinical judgment and the specific regulations in their jurisdiction.
3. Manufacturing and distribution: Pharmaceutical companies that produce stimulant medications must adhere to strict manufacturing standards and quality controls.

The distribution of stimulants is tightly regulated to prevent unauthorized access and reduce the risk of diversion to illicit markets. Governments may also implement monitoring systems, such as prescription drug monitoring programs, to track the prescribing and dispensing of stimulants.

4. Education and training: Health care professionals who prescribe stimulants are often required to undergo specific training and continuing education to enhance their understanding of the drugs, their potential side effects, and the appropriate prescribing practices. This helps ensure that stimulants are used responsibly and in accordance with established guidelines.
5. Monitoring and enforcement: Regulatory agencies, such as the FDA in the United States, monitor the safety and effectiveness of stimulant medications even after they have been approved for use. They may conduct post-marketing surveillance, review adverse event reports, and take necessary actions, including recalls or updates to labeling, if safety concerns arise.[65]

Co-use of Stimulants and Opioids

In recent years, the use of stimulants has increased among the population already using opioids, referred to as a "twin epidemic."[66] Even with the strict regulations of stimulant and opioid prescriptions, both opioid- and stimulant-related overdose deaths kept increasing. There is a concern about increasing co-exposures of stimulant and opioid in large populations and the subsequent consequences. One study suggested that the presence of fentanyl in methamphetamine and cocaine, which led to polysubstance use, could cause the increase in accidental overdose and death.[67] Results from the Substance Abuse and Mental Health Services Administration indicated that the stimulant–opioid combined substance use was involved in more than 50% of all stimulant-related overdose deaths.[68]

Studies have shown that many individuals who misuse opioids also use stimulants and vice versa.[69] The co-use of opioids and stimulants can synergistically reinforce the drug effects and the risk of overdose and other adverse health outcomes. The twin epidemic of opioid and stimulant abuse is particularly concerning because these drugs have different effects on the body and can interact in unpredictable ways.

Previous studies have shown that the co-use of these two types of drugs could synergistically reinforce dopamine signals and prolong the action of dopamine neuronal activities, leading to euphoric effects.[70] Despite the potential enhanced abuse risk of co-prescription of stimulant and opioid drugs, the United States does not restrict central nervous system stimulant prescriptions among patients with substance use disorder or under opioid treatment, whereas such regulation policy has been implemented in some north European countries.[71] To have a better understanding of the complexity of co-prescribing practices of opioids and stimulants, it is important to better understand patterns of long-term concurrent use of stimulants and opioids in large patient populations, such as co-prescribing prevalence and the likelihood of such a drug combination changes over time.

SUMMARY

Stimulant drugs are commonly used in the treatment of ADHD and narcolepsy. Stimulant medications can be addictive leading to stimulant use disorder with various clinical symptoms, including psychiatric and neurocognitive conditions, as well as negative social behaviors. Healthcare providers should carefully evaluate the patient's history and risk factors for substance abuse before prescribing stimulant drugs. Addressing the clinical complications related with stimulant use and stimulant use

disorder requires a comprehensive approach that includes prevention, treatment, and harm reduction strategies. These strategies should be tailored to the specific needs of individuals who are affected by the stimulants and should involve a multidisciplinary team of health care providers, public health officials, and community organizations.

DECLARATION OF INTERESTS

W Song, A Simona, P Zhang, DW Bates, and RD Urman conducted literature searches, wrote the article, and approved the final version. This review article complies with ethical standards. This article does not contain any studies with human or animal subjects performed by any of the authors.

FUNDING

Richard D. Urman received funding and/or fees from AcelRx, Merck, National Institutes of Health, and National Science Foundation.

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