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Review Article

Opioid, cannabinoid, cocaine, and methamphetamine epidemics: History, risk factors associated with them, and characteristics of drug action

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ABSTRACT

In the last century, mankind has made significant progress in the search and study of new pain-relieving drugs through the targeted synthesis of chemical analogs of natural opioids, cannabinoids, cocaine, and amphetamines. Experience with the medical use of new synthetic opioids, cannabinoids, and amphetamines has shown not only their high analgesic efficacy but also their high danger because of the risks of drug dependence and addiction, which have caused drug epidemics. The paper described the history of relevant drug epidemics, and the pharmacodynamics and pharmacokinetics of the most dangerous drugs, as well as the risks associated with drug epidemics, were outlined. Specifically, the risk of drug dependence to opioids, cannabinoids, amphetamine, and cocaine was not recognized until too late. Therefore, the drug crisis was initially largely iatrogenic. In recent decades, controls on the prescription of narcotic drugs have tightened; thus, drug addiction as iatrogeny occurs less frequently. However, criminal elements of society have established clandestine production of drugs and their realization in the youth and LGBT community disguising as new, fashionable designer drugs and devices for their use. Moreover, new synthetic drugs differ from natural drugs in their stronger psychostimulant effects, ability to cause addiction after the first use, and high risk of fatal poisoning. Thus far, no drugs were the treatment of opioid, cannabinoid, amphetamine, and cocaine abuse. However, the development of specific vaccines for these drugs has begun in recent years. Active immunization of drug abusers with specially created vaccines is expected to assist doctors in treating drug abusers in the future.

Keywords: cannabis; screw; pervitin; ecstasy; spice; vape; snus; hookahs; electronic cigarettes.

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Обзорная статья

Опиоидная, каннабиноидная, кокаиновая и метамфетаминовая эпидемии. История, факторы риска, связанные с ними, и особенности действия наркотиков

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АННОТАЦИЯ

Показано, что в последнее столетие человечество добилось значительных успехов в поиске и изучении новых болеутоляющих лекарственных средств путем целенаправленного синтеза химических аналогов природных опиоидов, каннабиноидов, кокаина и амфетаминов. Опыт медицинского применения новых синтетических опиоидов, каннабиноидов и амфетаминов показал не только их высокую болеутоляющую эффективность при болезнях, но и высокую опасность в связи с рисками развития лекарственной зависимости и наркомании, которые стали причиной наркотических эпидемий. Описывается история развития соответствующих наркотических эпидемий, указываются особенности фармакодинамики и фармакокинетики наиболее опасных наркотиков, а также риски, ассоциированные с наркотическими эпидемиями. В частности, указывается, что опасность развития лекарственной зависимости к опиоидам, каннабиноидам, амфетамину и кокаину была оценена с опозданием. В связи с этим первоначально наркотический кризис имел во многом ятрогенную природу. Однако в последние десятилетия контроль за назначением наркотических лекарственных средств ужесточился, поэтому наркомания как ятрогения возникает реже. Но криминальные элементы общества смогли наладить подпольное производство наркотиков и реализацию их в молодежной среде и в обществе ЛГБТ под видом новых, модных дизайнерских наркотиков и устройств их применения. Причем, новые синтетические наркотики отличаются от природных наркотиков более сильным психостимулирующим действием, способностью вызывать наркоманию после первых применений и высокой опасностью отравлений со смертельным исходом. Сообщается, что не существует одобренных лекарств для лечения наркоманов, злоупотребляющих опиоидами, каннабиноидами, амфетаминами и кокаином. Однако в последние годы начата разработка специальных вакцин от этих наркотиков. Предполагается, что в будущем активная вакцинация наркоманов специально созданными вакцинами поможет врачам в лечении наркоманов.

Ключевые слова: каннабис; винт; первитин; экстази; спайсы; вейпы; снюсы; кальяны; электронные сигареты.

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INTRODUCTION

Throughout history, humans have sought effective pain relief. The earliest pain medications were derived from plants such as mandrake, opium poppy, Indian hemp, and coca. These were prepared domestically and used alongside alcohol [1–3]. Opium, the dried milky juice of the soporific poppy plant (*Papaver somniferum*), has the longest documented history of use in medical anesthesia. A Sumerian clay tablet dating back to approximately 2100 BC, the world's oldest document of medical prescriptions, included the use of opium [3]. However, opium is a mixture of various chemicals, only some of which have a pain-relieving effect. For a long time, researchers have attempted to isolate the main painkilling substance of opium. In 1805, Friedrich Serturner succeeded in isolating such a substance — an alkaloid that was named "morphine" [4]. The name "morphine" was chosen to honor Morpheus, the Greek god of sleep and dreams, because of the substance's ability to induce sleep and cause visual hallucinations. Despite this, morphine was not widely used in medicine until 50 years after its discovery, when the development of the needle and syringe for subcutaneous injections made it more practical [4, 5]. Soon after, with the intravenous injections of morphine, its concentration in the blood quickly increased and exerted a significant effect on the body. However, simultaneous intravenous injections of morphine and its analgesic effect demonstrated several undesirable effects, including addiction and acute poisoning [6]. In the last century, the use of morphine and morphine-like substances by many patients led to the development of the opioid crisis (opioid epidemic) [7].

In the late 1800^{s}, cocaine, an anesthetic, was isolated from the sap of coca leaves and was initially recognized as an ideal energy booster. It was even added to tonic drinks. However, in the early 20th century, the uncontrolled use of cocaine led to addiction, which caused the cocaine crisis or "cocaine epidemic". Under public pressure, The Coca-Cola Company was forced to remove coca from the formulation of its popular drink. Even now, cocaine is still perceived as an extremely dangerous drug.

The medicinal use of cannabis dates back to ancient China, Egypt, and Greece, before the birth of Christ. However, it was not until 1964 in Israel that Meshulam and Gaoni isolated the main psychoactive substance of the plant, tetrahydrocannabinol (THC) [10]. In recent decades, THC analogs with more potent hallucinogenic and psychotropic effects have been synthesized. The rapid adoption of these newly synthesized cannabinoids resulted in addiction [11], leading to a widespread epidemic [12].

The first amphetamine epidemic was believed to have developed in the USA in the 1940^{s} and 1960^{s} because of inappropriate prescription, which was essentially iatrogenic. According to reports, the prevalence of drug dependence on amphetamines has remained at the same level as that in 1969, which was the peak of the epidemic [13–15]. The use of stimulants containing amphetamines and prescription stimulants is increasing in many countries across all age groups, particularly among adolescents and young adults [16–18].

HISTORY AND CAUSES OF THE OPIOID EPIDEMIC

Over the past century, the need for safer alternatives to the natural opioid morphine has led to the synthesis of many new morphine-like drugs (opioids or opiates). These compounds have similar biochemical and pharmacological effects, including the ability to induce feelings of relaxation, euphoria, and well-being. The pharmacological effects of morphine-like substances have found wide application in nonmedical and recreational purposes [19]. The ability of opioids to induce euphoria and improve mood has caused the development of psychiatric dependence.

Since the late 20th century, synthetic opioids have become increasingly popular as synthetic analogs of morphine because of their superior analgesic activity and reduced side effects, including transient hypersalivation, nausea, vomiting, defecation, and urination. The use of synthetic opioids in combination with neuroleptics (antipsychotic drugs) has become more popular in the medical community, a practice known as "neuroleptanalgesia" [20]. Synthetic opioids have become increasingly popular among drug abusers because of their higher efficacy and availability and their difficulty in detection through conventional testing technologies compared with classical opioids [21]. Fentanyl is the most commonly used synthetic opioid because of its analgesic effect, which is 50 times stronger than that of morphine. Analogs of fentanyl that exceed its activity and duration have been synthesized. Carfentanil, a fentanyl analog is reported to be 10,000 times more effective than morphine [22].

Since the 1990^{s}, the medical use of synthetic opioids has expanded. The prescription of opioid analgesics peaked in 2011 [23–35]. However, this led to the diversion of narcotic drugs from medical facilities, increased trafficking, drug abuse, and overdose deaths of patients and addicts. Currently, contemporary Western society is still in the midst of an opioid crisis (opioid epidemic) [26–30]. Opioid use, whether for medical or recreational purposes, has become a public health problem in some countries, including the USA [30].

The risk of drug overdose has reportedly increased because of the substitution of fentanyl and other synthetic opioids into heroin and counterfeit prescription opioid preparations without the user's knowledge. This is because drug traffickers market fentanyl and other new synthetic opioids as new psychoactive substances with desirable effects [31–34].

History and causes of the cannabinoid epidemic

In recent years, the interest in cannabinoids as hallucinogens within the addiction community has significantly increased [35]. Historically, these hallucinogens were primarily derived from marijuana, including cannabis, Indian cannabis, and wild hemp (*Cannabis sativa*). However, the synthetic production of these substances has become more prevalent [36, 37]. Compared with their synthetic counterparts, hemp herb and its extracts are more accessible to addicts because of the widespread availability of wild-growing hemp [38]. Individuals who are addicted to smoking mixtures containing parts of hemp plants, such as marijuana, cannabis, or hashish, inhale the smoke. Inhalation of smoke from a lit smoking mixture containing cannabis herb, leaves, stems, and/or inflorescences can cause symptoms of acute poisoning in a healthy person without addiction or dependence. However, an addict may experience drug intoxication. Signs of poisoning with mood deterioration or narcotic action with mood improvement typically appear within 15–20 s, reach a maximum in 10–30 min, and then gradually decrease over 1–3 h. Cannabinoid poisoning can cause various symptoms in healthy individuals (not an addict), including nausea, vomiting, dizziness, confusion, unsteady gait, weakness, tachycardia, hypertension, dry mouth, mydriasis, photophobia, seizures, auditory and visual hallucinations, and mood deterioration with fear and nightmares. When administered to an addict, cannabinoids can induce narcotic intoxication. This is characterized by an improved mood, disappearance of feelings of fatigue and irritability, and emergence of feelings of joy and cheerfulness. In addition, auditory and visual hallucinations and inappropriate behavior may develop.

In recent years, various ready-to-use fumigation mixtures and incense, often containing synthetic cannabinoids with intoxicating effects, have become nearly ubiquitous. The most well-known products are spice, vape, snus, hookahs, and e-cigarettes [39]. E-cigarettes, or e-hookahs, are long, pen-like devices for vaping (inhaling vapor) that were introduced to the US market in 2014 and are highly sought after by adolescents and young adults [39–41]. The use of cannabinoid flavor blends is expanding because of a widespread public perception that e-cigarettes are less harmful to health than conventional cigarettes.

Concurrently, cannabinoids are widely used because of their sedative effects, neuroprotective properties, mood enhancement effects, appetite stimulation effects, antiemetic properties, analgesic effects, muscle relaxation effects, immunosuppressive properties, reduction of inflammation and allergy symptoms, intraocular pressure reduction, bronchial dilation, and antitumor effects [41–44]. Following the discovery that tetrahydrocannabinol was the primary psychoactive substance in cannabis extract, drug traffickers gained access to information on its chemical structure and synthesis. Consequently, cannabinoids are now synthesized in clandestine laboratories and sold on the illicit drug market as designer drugs. In the early 2000s, synthetic cannabinoids became available and popular under brand names such as Spice and K2. This was partly attributed to their ability to avoid detection by standard cannabinoid screening tests [45, 46].

Illicitly produced synthetic cannabinoids, also known as designer drugs, can be 2–100 times more potent hallucinogens than THC [44]. Some may also have more potent analgesic, anticonvulsant, anti-inflammatory, and anticancer effects [45]. However, synthetic cannabinoids can cause various medical and psychiatric emergencies because of their physiological and psychoactive effects, which are similar to those of THC but more intense. These emergencies may include acute renal failure, psychosis, and suicidal ideation [46]. Nausea, vomiting, dyspnea, depressed respiration, hypertension, tachycardia, chest pain, and muscle twitching may develop independently [44, 47, 48].

History and causes of the methamphetamine epidemic

Methamphetamine, also known as amferoxin, gerovit, sondrex, dezamine, methedrine, and neodrine, and commonly referred to as “meth”, “ice”, or “crystal glass”, is a powerful hallucinogenic drug that belongs to the group of psychostimulants and is chemically related to ephedrine-type amphetamines. Over the past 50 years, amphetamines have been classified as illicitly trafficked drugs in many countries, leading to restricted access [49]. However, pharmacies still sell drugs such as naftisin, sanorin, galazolin (runny nose drops), and solutan (bronchospasm remedy), which contain substances with chemical structure and pharmacological effects similar to ephedrine. This has led to the production of a drug with effects similar to those of methamphetamine in the criminal environment [50]. Methamphetamine is synthesized clandestinely from ephedrine and its analogs using reductive reactions. The Birch, Nagai, Leuckart, and Emde methods are commonly used under unsanitary conditions with pseudoreactants such as battery acid, sewage cleaner, potassium permanganate, and antifreeze. The resulting drug is a crystalline substance that appears as clear, fairly large crystals or shiny bluish-white stones. The drug referred to by addicts as “vint” or “npervitin” is not a pure amphetamine.

The injection of chemically impure methamphetamine is associated with the development of postinjection necrosis at the injection site. Methamphetamine users have reported serious adverse effects and incidents of fires, explosions, and toxic waste from methamphetamine laboratories that pose a threat to human welfare [51].

The drug’s most concerning attribute is its potential to cause addiction after just one use. Therefore, homemade “pervitin” should not be considered a medical pervitin analog created using pure methamphetamine. Instead,

it is more appropriate to refer to homemade pervitin by its slang name "vint." In recent years, the synthetic drug 3,4-methylenedioxymethamphetamine has been included in "vint" or used as a substitute. Illicit distribution of drugs commonly referred to as "ecstasy" or "Molly" (the latter being slang for "molecular") frequently occurs in nightclubs and dance parties, also known as "raves." These drugs are also commonly referred to as "club drugs". Because of the lack of quality control, users may be unaware of the exact composition of the substance they have ingested [50].

The methamphetamine epidemic, which began during World War II, was associated with the widespread use of the medical drug pervitin and was iatrogenic [13–18]. Currently, the prevalence of methamphetamine addiction continues to increase annually. The current methamphetamine epidemic has contributed to more overdose deaths than the opioid epidemic. In 2021, methamphetamine was ranked among the top 10 deadliest drugs in the USA [49, 52].

The pharmacodynamics of amphetamines are attributed to the release of catecholamines into the bloodstream from the adrenal glands and the stimulation of adrenoreceptors. Consequently, the pharmacological effects of amphetamines align with those of adrenaline and noradrenaline. Amphetamines increase the reactivity of the organism, basic metabolism, heart rate, and activity of the central nervous system, respiratory system, and skeletal muscles. They also decrease the functional activity of the digestive organs. In addition, amphetamines increase the blood flow to the brain and heart muscles. They are considered doping because they enhance the mental and physical performance of athletes, which may violate sports ethics [51].

The pharmacological effects of therapeutic doses of amphetamines, when first administered to individuals not addicted to amphetamines and hallucinogens, are characterized by mydriasis, photophobia, oral and nasal dryness, sore throat, bronchial dilation, inability to sit still, increased mental and physical performance, improved senses (smell, hearing, and vision), elimination of fatigue and drowsiness, and suppression of smooth muscles and gastrointestinal glands [52–54]. Tachycardia and hypertension may also occur. Toxic doses of amphetamines can exert various negative effects, including insomnia, mental and physical hyperactivity, paranoia, hallucinations, illusions of omnipotence, increased aggression, anxiety, fear, and violent behavior. In some cases, seizures and convulsions may occur, which can be fatal. Inadequate behavior may develop when a person is unable to sit still and has an irrepressible desire to run away from someone. This can lead to situations where a person in fear runs for a long time through a dark forest in an unknown direction, not feeling tired or pain from the branches and with clothes torn by the tree branches. Sometimes, such behavior can result in death because of accidental injury or exhaustion. This is because a period of excessive excitement is often followed by a period of complete weakness and sleep. In some cases, the patient's condition may resemble an acute attack of schizophrenia [50–55].

Amphetamine addiction is characterized by the inability to function normally without regular and repeated use of the drug. Addicts often describe their lives as a constant attempt to escape the fear of death. The drug is typically injected intravenously, causing immediate excitement and sometimes aggression toward others. This stage can last up to 30 min. After the initial stage of narcotic intoxication, which lasts for 4–16 h, the user enters a stage of uncontrolled drug use characterized by a desire to prolong the euphoria. During this stage, addicts seek to take an additional dose of the drug. This state can last for 3–15 days. During this period, the addict experiences an increase in mental, intellectual, and physical activity. However, a subsequent phase develops in which additional doses of the drug no longer produce euphoria or narcotic intoxication. Instead, the addict's body craves sleep, leading to insomnia and potentially resulting in psychosis, hallucinations, irritability, and aggressiveness. This can make the addict dangerous to others and may cause injury. As addicts fall asleep, they remain in deep sleep for 1–3 days. During this period, they are practically immobile and do not pose a threat to others. Upon waking up, the person may feel sleep-deprived and hungry. The addict may experience dehydration, physical, mental, and emotional exhaustion, and depression. They may lose the ability to experience pleasure without the drug and may even have suicidal thoughts. This period typically lasts between 2 and 14 days, during which the addict's primary focus is to take another dose of methamphetamine (vint) [50–55].

In recent years, a study reported an increase in the use of combinations of stimulants and opioids among methamphetamine addicts [56]. Regrettably, this has resulted in a rise in deaths caused by simultaneous overdoses of amphetamines and synthetic opioids [57].

The current methamphetamine epidemic has led to an increased preoccupation with the drug among lesbian, gay, bisexual, and transgender (LGBT) individuals because of its ability to enhance sexual feelings. This has resulted in mobile advertising of the drug through a mobile application used by members of the LGBT community, which has expanded the geographic location of drug users [58–61]. In addition, acquired immunodeficiency syndrome is a risk factor associated with methamphetamine addiction because people with human immunodeficiency virus infection try to improve their mood with such drugs [62, 63].

CONCLUSIONS

Over the past century, significant progress has been made in the chemical modernization of pain medications through the synthesis of compounds that are analogs of natural opioids, cannabinoids, cocaine, and amphetamines.

Synthetic analogs of these pain medications are highly useful in medicine but also highly dangerous, increasing the risk of drug and substance dependence. Assessment of the risk of developing drug dependence to opioids, cannabinoids, amphetamine, and cocaine was delayed. Accordingly, the drug crisis was initially largely iatrogenic. In recent decades, the prescription of narcotic drugs has been strictly controlled to reduce the likelihood of medical professionals and the drugs themselves from causing drug dependence. However, criminal elements have become more active during this time, establishing clandestine drug production and distribution, particularly targeting the youth and LGBT communities by marketing new and fashionable drugs and devices. Moreover, synthetic drugs differ from natural drugs in their stronger psychostimulant effect, ability to cause addiction after the first use, and high risk of fatal poisoning.

Currently, no medications have been approved for treating opioid, cannabinoid, amphetamine, and cocaine abuse. However, active immunization with specially developed vaccines may offer hope for combating drug epidemics in the future [64–67]. The initial results from experimental studies are promising. Advances in the development of vaccine conjugates, use of carrier proteins, and optimization of adjuvants are expected to allow the production of the "right" drug antibodies in drug abusers. With high levels of high-quality antibody production, drug vaccines could become clinical tools for treating substance abuse [68].

ADDITIONAL INFORMATION

Authors contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. The contribution of each author: A.L. Urakov, P.D. Shabanov — manuscript drafting, writing and pilot data analyses, general concept discussion.

Competing interests. The authors declare that they have no competing interests.

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