American Journal of Medicine and Medical Sciences 2025, 15(3): 647-652
DOI: 10.5923/j.ajmms.20251503.34

Features of Combined Abuse of Traditional Opioids and New Psychostimulants

Mukaddas Sherxanovna Rustamova[1], Lyudmila Aleksandrovna Tursunxodjayeva[2], Jakhongir Azimjon Ugli Ravshanov[3,*]

[1]Independent Researcher, Department of Narcology and Adolescent Psychopathology, Center for the Development of Professional Qualifications of Medical Workers, Tashkent, Uzbekistan
[2]DSc, Professor, Department of Narcology and Adolescent Psychopathology, Center for the Development of Professional Qualifications of Medical Workers, Tashkent, Uzbekistan
[3]Assistant, Department of Psychiatry and Narcology, Tashkent Medical Academy, Tashkent, Uzbekistan

Abstract Polysubstance abuse involving synthetic cathinones and traditional opioids is an increasing concern in addiction medicine. This type of dependence is characterized by rapid tolerance development, severe somatic and psychiatric complications, and a high relapse rate. The article examines epidemiological aspects, neurobiological mechanisms of addiction formation, clinical manifestations, and modern treatment approaches. Due to the complex nature of this addiction, a multidisciplinary approach is required, including pharmacotherapy, psychotherapy, and social rehabilitation. Further research is needed to optimize therapeutic strategies and prevent relapses.

Keywords Polysubstance abuse, Synthetic cathinones, Opioids, Addiction, Neurobiology, Treatment, Rehabilitation

1. Introduction

Polysubstance abuse is diagnosed when dependence on two or more narcotic substances is detected, used simultaneously or in a certain sequence. Polysubstance abuse is a qualitatively new condition, different from the corresponding monodrug addictions. According to research, this condition has features of formation, course, clinical manifestations, withdrawal syndrome, medical and social consequences.

Three types of consumption of two or more drugs have been identified:

- combined use – simultaneous administration of two or more drugs or use of the next drug in a state of intoxication with the previous one;
- intermittent use – use of the next drug immediately after the effect of the previous one has ended;
- periodic use – alternating periods of use of different drugs or their combinations [1,35,36].

Polysubstance abuse and complicated monodrug abuse may occur at the stage of drug selection, at one of the subsequent stages, or be the outcome of the disease. The reasons for switching to additional intake of another psychoactive substance may be:

- disappearance of the desired euphoria from the original substance due to increasing tolerance;
- persistent insomnia requiring the use of sedatives and hypnotics;
- difficult availability of the original psychoactive substance;
- the need to eliminate withdrawal disorders caused by the withdrawal of the original psychoactive substance [2,3,4].

When abusing stimulants and opioids, a person takes the psychoactive substance repeatedly to experience the same euphoria. During this time, the person is disconnected from family, work, and social life. This continuous drug use continues until the person is physically and mentally exhausted [5,6,8].

2. Objectives

This study aims to analyze the epidemiological aspects, neurobiological mechanisms of addiction formation, clinical manifestations, and modern treatment approaches for polysubstance abuse involving synthetic cathinones and opioids.

3. Methods

The study is based on a review of relevant literature from scientific journals, clinical studies, and reports from international organizations. Epidemiological data were obtained from

* Corresponding author:
ravshanovjakhongir9@gmail.com (Jakhongir Azimjon Ugli Ravshanov)
Received: Feb. 19, 2025; Accepted: Mar. 9, 2025; Published: Mar. 11, 2025
Published online at http://journal.sapub.org/ajmms

UNODC reports, while neurobiological and clinical aspects were analyzed through a review of previously published experimental and clinical studies. The methodology includes:

- Review of historical trends and current epidemiology of opioid and stimulant addiction.
- Analysis of neurobiological mechanisms of addiction formation.
- Examination of clinical manifestations and treatment approaches.

4. Results

Brief Historical Overview of Opioid and Stimulant Addiction

Opioid addiction has a long history, dating back to the use of opium in ancient civilizations. Over time, heroin was synthesized, gaining popularity in the 20th century and triggering waves of addiction epidemics [9].

Simultaneously, stimulants (amphetamines) emerged in medicine, initially prescribed for the treatment of asthma, narcolepsy, and even depressive conditions. However, recreational use of these substances became widespread over time. Later, synthetic analogs such as methamphetamine and cathinones appeared, rapidly spreading on the illicit drug market [10].

Modern Epidemiology of Polydrug Use

According to UNODC, the proportion of individuals using multiple psychoactive substances (PAS) is increasing across most drug markets. The combination of opioids and psychostimulants is particularly common, as it enhances euphoria, "compensates" for the undesirable effects of one substance with another, and induces cross-tolerance [11,39].

Young people are at the highest risk of polydrug use due to the easy availability of substances online and the influence of social networks [12].

Socioeconomic Consequences

The combined abuse of opioids and stimulants places a significant burden on healthcare systems, law enforcement agencies, and social services [13]. The rising number of overdoses and severe complications necessitates the expansion of toxicology departments and intensive care unit (ICU) beds.

Moreover, individuals struggling with polydrug addiction often lose social connections, face unemployment, and experience family breakdowns, further deepening marginalization and stigmatization. Consequently, polydrug addiction is not only a medical issue but also a pressing social problem.

Neurobiological Mechanisms of Addiction

General Mechanisms of Addiction Formation

Substance use disorder is associated with the activation of the mesolimbic reward system, which includes the ventral tegmental area (VTA), nucleus accumbens, and medial prefrontal cortex. An increased release of dopamine in these regions reinforces pleasure perception and induces pathological neuroplasticity, contributing to addiction development [9].

In polydrug addiction, tolerance formation occurs more rapidly due to the divergent effects of different substances, which simultaneously engage various neurochemical pathways [14].

Role of the Dynorphin/Kappa-Opioid System

The dynorphin/kappa-opioid receptor (KOR) system plays a key role in modulating addiction. Dynorphin, an endogenous opioid peptide, binds to kappa-opioid receptors, activating a negative feedback system that suppresses excessive dopaminergic activity. This mechanism helps stabilize neurotransmission, but under chronic exposure to psychoactive substances (PAS), it leads to dysphoria, anxiety, and depression.

Clinical studies indicate that the administration of KOR antagonists can reduce the severity of these symptoms and lower the risk of relapse [14].

Effects of Combined Substance Use

The simultaneous use of opioids and psychostimulants results in complex interactions, leading to an enhanced euphoric effect and a higher risk of addiction. Opioids activate mu-opioid receptors, inhibiting the release of excitatory neurotransmitters such as glutamate, which produces a sedative effect. In contrast, psychostimulants increase the release of dopamine and norepinephrine, inducing alertness and energy.

This combination causes pathological hyperactivation of the mesolimbic system, which accelerates addiction development and exacerbates cognitive impairments [14].

Characteristics of Opioid Addiction

Opioids activate mu-opioid receptors, leading to a decrease in the release of excitatory neurotransmitters, such as glutamate, and an increase in gamma-aminobutyric acid (GABA) levels. This results in analgesia, sedation, and euphoria.

Prolonged opioid use causes mu-receptor desensitization, leading to the development of tolerance. Additionally, it suppresses adenylate cyclase pathway activity, which explains the severe withdrawal symptoms, including pain, tachycardia, and chills [15].

Characteristics of Psychostimulant Addiction

Psychostimulants enhance catecholamine (dopamine and, to a lesser extent, norepinephrine) neurotransmission by directly increasing synaptic concentrations of neurotransmitters, and are generally divided into two categories: reuptake inhibitors and catecholamine release stimulants.

Reuptake inhibitors block the transport proteins responsible for transporting the released neurotransmitter back to the presynaptic neuron for elimination and recycling, thereby increasing the synaptic concentration of that neurotransmitter. [16,17,19,20,21,22,23,24] Mephedrone has additionally been shown to mediate monoamine release via organic cation transporter 3 (OCT3), indicating that cathinones target both high-affinity and low-affinity/high-

capacity transporters [21]. Similar to amphetamines, cathinone designer drugs also interact with several adrenergic and serotonergic receptors [19,20,21,24]. Compared with amphetamines, however, cathinone designer drugs have been shown to interact less potently with TAAR1 and VMAT2 [16,25] These less potent interactions at TAAR1 may result in a higher risk of cathinone depen dence compared with amphetamines. This leads to increased energy, heightened motivation, and euphoria. However, prolonged use depletes neurotransmitter reserves, resulting in the development of depressive states and cognitive impairments. Chronic use also leads to dopamine receptor depletion, which further exacerbates depression and cognitive dysfunction [26].

Additionally, the anxiogenic potential of stimulants, along with paranoid and psychotic episodes, makes treatment more challenging.

Neurobiology of Combined Substance Use

The simultaneous use of opioids and psychostimulants produces both synergistic and opposing effects**.** Opioids reduce anxiety and arousal, which can dampen the acute stimulation caused by psychostimulants. However, their combined use significantly enhances dopamine release in the reward system, leading to intense euphoria and rapid addiction development [14].

At the neuronal level, polydrug use amplifies synaptic plasticity alterations. Studies show that in the hippocampus and prefrontal cortex, there is an increase in abnormal dendritic spines, which is linked to impaired long-term memory formation and reduced impulse control. These changes contribute to aggression, cognitive decline, and behavioral disorders in affected individuals [26]. Clinical Features of Combined Addiction.

The dangers of polydrug use compared to monodrug use are:

Patients are more likely to inject drugs, which increases the risk of viral hepatitis and other infectious diseases. [1,27,28,30].

Poverty due to the social consequences.

Co-use of opioids and stimulants poses significant challenges to health systems, law enforcement, and social structures [1,31].

The lack of specialized medications to relieve stimulant cravings complicates therapy [1,32].

Types of Clinical Progression

Opioid-stimulant addiction, though relatively "rare" in early epidemiological studies, has recently been recognized as one of the most aggressive forms of substance use disorder. It is characterized by rapid tolerance development, severe withdrawal symptoms, and pronounced mental dysfunction. In the early stages of addiction, patients often engage in combined use of opioids (heroin, methadone, tramadol) and psychostimulants (cocaine, amphetamine, methamphetamine, synthetic cathinones) to enhance euphoria or counterbalance the side effects of one substance with another [39] A false compensation phenomenon is frequently observed in the initial phase of combined dependence:

- The sedative-analgesic effects of opioids may temporarily mitigate the negative symptoms induced by excessive stimulation.
- Conversely, psychostimulants help patients overcome drowsiness and lethargy, which are typical post-injection or post-intake effects of opioids. Patients report that their usual drug doses become insufficient, prompting them to significantly increase the amount of both opioids and stimulants within just a few weeks or months. Stimulants are often used as a “corrector” for opioid side effects, and vice versa [9].

This pattern results in the rapid formation of both physical and psychological dependence. Many patients subjectively feel more confident when regularly combining opioids and stimulants, believing that this prevents extreme sedation or excessive agitation.

However, clinical experience suggests that even in the early stages, this self-regulation strategy can lead to:

- Sleep disturbances,
- Hidden cardiovascular complications (arrhythmias, blood pressure fluctuations),
- Psychiatric decompensation (depressive episodes, irritability, aggression).

Tolerance accumulation progresses faster than in monosubstance addiction, leading patients to reach the late, more severe stage of polydrug addiction much sooner [39].

Late-Stage Characteristics

The late stage of combined opioid-stimulant addiction is marked by:

- Progressive physical and psychological deterioration,
- More severe withdrawal syndromes,
- Intensified pathological cravings.

The opioid component of the addiction produces classical withdrawal symptoms, such as:

- Severe muscle pain and body aches,
- Dilated pupils,
- Excessive sweating,
- Autonomic instability.

Meanwhile, stimulant withdrawal is characterized by:

- Depressive episodes,
- Severe apathy,
- Psychomotor retardation,
- Significant reduction in energy levels [9],
- The simultaneous presence of both withdrawal syndromes creates a polymorphic clinical picture, with symptoms varying between:
- Somatovegetative manifestations (nausea, vomiting, tachycardia, tremors),
- Psychopathological symptoms (severe depression, anxiety disorders, sometimes delirious or paranoid psychotic episodes) Increased Suicide Risk in Late-Stage Polydrug Addiction.

During the late stages of polydrug addiction, the risk of suicidal behavior significantly increases, driven by:

- Severe physical deterioration,
- Unbearable withdrawal symptoms,
- An acute psychoemotional crisis—patients become unable to "relieve" their internal suffering with either substance, as tolerance levels are extremely high, and adverse effects outweigh any euphoric potential [9,34],
- Social maladaptation, including loss of meaningful relationships, family breakdown, and inability to work, further exacerbates the clinical picture. This creates a vicious cycle in which the patient is compelled to continue substance use due to both somatic and psychological pressures.

Thus, the clinical progression of opioid-stimulant addiction can be divided into two key stages:

1. Early Stage
   - o Rapid tolerance escalation,
   - o Compensatory use (patients use one substance to counteract the side effects of another),
   - o Formation of persistent dual dependence.
2. Late Stage
   - o Severe physical and psychological distress,
   - o Overlapping withdrawal syndromes,
   - o Increased risk of severe complications and fatal outcomes,
   - o This clinical specificity highlights the need for specialized diagnostic approaches, including:
     - Recognition of multi-substance use,
     - Comprehensive mental health assessment.

Additionally, treatment strategies must be multidisciplinary, integrating:

- Pharmacotherapy,
- Psychotherapy,
- Social rehabilitation measures.

Opioid-stimulant addiction develops at both early and late stages of substance abuse. It is distinguished by rapid tolerance buildup and a severe withdrawal syndrome [9].

In the early stage, patients may attempt to "compensate" for the effects of one substance with another.

- In the late stage, full-fledged polydrug addiction develops, increasing the risk of acute cardiovascular complications and psychiatric disorders.

Cognitive and psychotic impairment

Co-dependency causes more severe impairments in attention, memory, executive functions and a higher risk of psychotic states [11,13] Dopaminergic overdrive from stimulants and the sedative effect of opioids mutually reinforce the disorganization of neural networks [33].

Promising research directions

Further study of the pathogenesis of combined addiction, including cross-processes of neuroadaptation, the role of genetic factors and the influence of stress-axis HPA [11] seems promising. Of particular interest is the development and implementation of special therapeutic regimens that include pharmacological correction of two types of withdrawal syndrome at once, as well as testing adapted psychotherapeutic modules. International institutes (NIDA, EMCDDA) emphasize the need for multicenter studies to develop unified recommendations [12].

5. Discussion and Conclusions

Polydrug addiction, which begins with the abuse of stimulants, develops in a shorter time than with the initial use of opiates. More severe psychopathic changes, memory and intellect disorders develop.

In general, the combined abuse of opiates and psychostimulants worsens the course of drug addiction, the number of severe somatoneurological complications increases, and personality changes occur quickly.

The literature review suggests a need for further research to fill gaps in understanding the pathophysiology and clinical specificity of opioid-stimulant co-use and to facilitate the development of effective treatment, rehabilitation and relapse prevention regimens.

REFERENCES

[1] ADAI. Opioids and Stimulants: What Are They and How Are People Using Them? April 2021 \ K. Michelle Peavy, PhD; Caleb Banta-Green, PhD, MPH, MSW; Mandy Owens, PhD.

[2] May, A. C., Aupperle, R. L., & Stewart, J. L. (2020). Dark Times: The Role of Negative Reinforcement in Methamphetamine Addiction. Frontiers in Psychiatry, 11.

[3] Cicero, T. J., & Ellis, M. S. (2017). The prescription opioid epidemic: a review of qualitative studies on the progression from initial use to abuse. Dialogues in clinical neuroscience, 19(3), 259.

[4] Hartwell, K. J., Back, S. E., McRae-Clark, A. L., Shaftman, S. R., & Brady, K. T. (2012). Motives for using: a comparison of prescription opioid, marijuana and cocaine dependent individuals. Addictive behaviors, 37(4), 373-378.

[5] Cheng, W. S., Garfein, R. S., Semple, S. J., Strathdee, S. A., Zians, J. K., & Patterson, T. L. (2010). Binge use and sex and drug use behaviors among HIV (–), heterosexual methamphetamine users in San Diego. Substance use & misuse, 45(1-2), 116 133.

[6] Roy, É., Arruda, N., Jutras-Aswad, D., Berbiche, D., Perreault, M., Bertrand, K., ... & Bruneau, J. (2017). Examining the link between cocaine binging and individual, social and behavioral factors among street-based cocaine users. Addictive behaviors, 68, 66-72.

[7] Lende, D. H., Leonard, T., Sterk, C. E., & Elifson, K. (2007). Functional methamphetamine use: The insider's perspective. Addiction Research & Theory, 15(5), 465-477.

[8] Díaz, R. M., Heckert, A. L., & Sánchez, J. (2005). Reasons for stimulant use among lation gay men in San Francisco: A comparison between methamphetamine and cocaine users. Journal of Urban Health, 82(1), i71-i78.

[9] Koob G.F., Volkow N.D. (2016). Neurobiology of addiction: a neurocircuitry analysis. The Lancet Psychiatry, 3(8), 760–773.

[10] Murray J.B., Kores R.C., Denton R. (2018). Neuropsychological analysis of chronic polydrug use: The interplay of opioids and stimulants. Behavioral Neuroscience, 132(1), 85–91.

[11] Green R., Gregor C., Wood J. (2016). Polydrug use, psychostimulants, and negative health outcomes. Addiction Biology, 21(2), 201–213.

[12] EMCDDA (2020). European Monitoring Centre for Drugs and Drug Addiction. Annual Report. Luxembourg: Publications Office of the European Union.

[13] Heinzerling K.G., Ober A., Lamp K. (2019). Pharmacotherapies for treatment of stimulant use disorders. Addiction Science & Clinical Practice, 14(1), 517–525.

[14] Shagiahmetov R.S., Proskuryakova E.P. (2015). Динорфин/каппа-опиоидная система и стрессовая модуляция наркологических расстройств. Наркология, 6, 286–291.

[15] Shustov D.I., Kiselev S.V. (2020). Физические проявления толерантности и абстиненции при опиоидной зависимости. Наркология, (3), 39–45.

[16] Eshleman AJ, Wolfrum KM, Hatfield MG, Johnson RA, Murphy KV, Janowsky A (2013) Substituted methcathinones differ in trans porter and receptor interactions. Biochem Pharmacol 85(12): 1803–1815. https://doi.org/10.1016/j.bcp. 2013.04.004.

[17] Baumann MH, Partilla JS, Lehner KR (2013) Psychoactive ‘‘bath salts’’: not so soothing. Eur J Pharmacol 698(1–3):1–5. https://doi.org/10.1016/j.ejphar.2012.11.020.

[18] Luethi D, Trachsel D, Hoener MC, Liechti ME (2018d) Monoamine receptor interaction profiles of 4-thio-substituted phenethylami nes (2C-T drugs). Neuropharmacology 134(Pt A): 141–148. https://doi.org/10.1016/j.neuropharm.2017.07.012.

[19] Luethi D, Kolaczynska KE, Docci L, Kra¨henbu¨hl S, Hoener MC, Liechti ME (2018c) Pharmacological profile of mephedrone analogs and related new psychoactive substances. Neurophar macology 134(Pt A):4–12. https://doi.org/10.1016 /j.neuropharm. 2017.07.026.

[20] Mayer FP, Wimmer L, Dillon-Carter O, Partilla JS, Burchardt NV, Mihovilovic MD, Baumann MH, Sitte HH (2016) Phase I metabolites of mephedrone display biological activity as substrates at monoamine transporters. Br J Pharmacol 173(17): 2657–2668. https://doi.org/10.1111/bph.13547.

[21] Mayer FP, Cintulova D, Pittrich DA, Wimmer L, Luethi D, Holy M, Jaentsch K, Tischberger S, Gmeiner G, Hoener MC, Liechti ME, Mihovilovic MD, Sitte HH (2019a) Stereochemistry of phase-1 metabolites of mephedrone determines their effectiveness as releasers at the serotonin transporter. Neuropharmacology 148: 199–209. https://doi.org/10.1016/j. neuropharm.2018.12.032.

[22] Niello M, Cintulova D, Hellsberg E, Ja¨ntsch K, Holy M, Ayatollahi LH, Cozzi NV, Freissmuth M, Sandtner W, Ecker GF, Mihovilovic MD, Sitte HH (2019) para-Trifluoromethyl -meth cathinone is an allosteric modulator of the serotonin transporter. Neuropharmacology 161:107615. https://doi.org/ 10.1016/j.neuro pharm.2019.04.021.

[23] Rickli A, Hoener MC, Liechti ME (2015a) Monoamine transporter and receptor interaction profiles of novel psychoactive sub stances: para-halogenated amphetamines and pyrovalerone cathinones. Eur Neuropsychopharmacol 24(3): 365–376. https://doi.org/10.1016/j.euroneuro.2014.12. 012.

[24] Simmler LD, Buser TA, Donzelli M, Schramm Y, Dieu LH, Huwyler J, Chaboz S, Hoener MC, Liechti ME (2013) Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol 168(2): 458–470. https://doi.org/10.11 11/j.1476-5381.2012. 02145.x.

[25] Simmler LD, Buchy D, Chaboz S, Hoener MC, Liechti ME (2016) In vitro characterization of psychoactive substances at rat, mouse, and human trace amine-associated receptor 1. J Pharma col Exp Ther 357(1): 134–144. https://doi.org/10.11 24/jpet.115. 229765.

[26] Volkov M.V., Spirin A.S. (2015). Изменения дофаминовых рецепторов D2 при систематическом употреблении психостимуляторов. Вопросы наркологии, (4), 23–27.

[27] Daniulaityte, R., Silverstein, S. M., Crawford, T. N., Martins, S. S., Zule, W., Zaragoza, A. J., & Carlson, R. G. (2020). Methamphetamine use and its correlates among individuals with opioid use disorder in a midwestern US city. Substance Use & Misuse, 1-9.

[28] Glick, S. N., Burt, R., Kummer, K., Tinsley, J., Banta-Green, C. J., & Golden, M. R. (2018). Increasing methamphetamine injection among non-MSM who inject drugs in King County, Washington. Drug and alcohol dependence, 182, 86-92.

[29] Chawarski, M. C., Hawk, K., Edelman, E. J., O'Connor, P., Owens, P., Martel, S., ... & Cowan, E. (2020). Use of amphetamine type stimulants among emergency department patients with untreated opioid use disorder. Annals of emergency medicine, 76(6), 782-787.

[30] Shearer, R. D., Howell, B. A., Bart, G., & Winkelman, T. N. (2020). Substance use patterns and health profiles among US adults who use opioids, methamphetamine, or both, 2015-2018. Drug and alcohol dependence, 214, 108162.

[31] Timko, C., Han, X., Woodhead, E., Shelley, A., & Cucciare, M. A. (2018). Polysubstance use by stimulant users: health outcomes over three years. Journal of studies on alcohol and drugs, 79(5), 799-807.

[32] Wang, L., Min, J. E., Krebs, E., Evans, E., Huang, D., Liu, L., ... & Nosyk, B. (2017). Polydrug use and its association with drug treatment outcomes among primary heroin, methamphetamine, and cocaine users. International Journal of Drug Policy, 49, 32-40.

[33] Sofuoglu M., Carroll K.M., Petry N.M. (2020). Pharmacological and behavioral treatment of opioid–stimulant polysubstance use. Current Opinion in Psychiatry, 33(4), 74–80.

[34] Petry N.M., Bickel W.K. (2013). Polydrug abuse and addiction. Behavioral Pharmacology, 24(1), 19–21.

[35] Al-Tayyib et al., "Heroin and Methamphetamine Injection: An Emerging Drug Use Pattern," Substance Use & Misuse 52, no. 8 (2017): 1051.

[36] J. Ondocsin et al., "The Motives and Methods of Methamphetamine and 'Heroin' Co-Use in West Virginia," Harm Reduction Journal 20, no. 1 (2023).

[37] Winstock, A.; Mitcheson, L.; Ramsey, J.; Davies, S.;

Puchnarewicz, M.; Marsden, J. Mephedrone: Use, subjective e ects and health risks. Addiction 2011, 106, 1991–1996. [CrossRef] [PubMed]

[38] Schmoll, S.; Romanek, K.; Stich, R.; Bekka, E.; Stenzel, J.; Geith, S.; Eyer, F.; Rabe, C. An internet-based survey of 96 German-speaking users of "bath salts": Frequent complications, risky sexual behavior, violence, and delinquency. Clin. Toxicol. (Phila) 2018, 56, 219–222. [CrossRef]

[39] Mistry C.J., Bawor M., Desai D., Marsh D.C., Samaan Z. (2014). Genetics of opioid dependence: A review of the genetic contribution to opioid dependence. Current Psychiatry Reviews, 10(2), 156–167.