

# Cardiac manifestations of post-acute withdrawal syndrome from a history of synthetic cathinone and opioid use

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## ABSTRACT

**Introduction:** Synthetic cathinones and opioids are among the most commonly used illicit drugs in Central Asia, including Kazakhstan. Despite the advent of synthetic cathinones, opioids have not lost their relevance. Patients frequently report poly-dependence, combining cathinones and opioids. The use of synthetic cathinones and opioids is associated with cardiovascular disease and cardiovascular mortality. However, there is limited data describing the cardiac effects of synthetic cathinones and opioids in patients with post-acute withdrawal syndrome. The aim of this work is to describe and compare the cardiac manifestations in patients using synthetic cathinones and opioids with post-acute withdrawal syndrome.

**Materials and Methods:** In this case-control study, we examined 294 patients over the age of 18 who were using synthetic cathinones and opioids. All patients underwent electrocardiography and transthoracic echocardiography.

**Results:** Our study involved 183 patients using synthetic cathinones and 111 patients reporting opioid use. The average age of the patients was  $32.4 \pm 8.5$  years. In patients using synthetic cathinones, electrocardiography showed a lengthening in the average duration of the ventricular QRS complex ( $70.5 \pm 13.3$  ms vs.  $69.6 \pm 11.7$  ms), T wave ( $154.1 \pm 27.5$  ms vs.  $140.4 \pm 24.1$  ms), and QT interval ( $338.2 \pm 28.5$  ms vs.  $334.8 \pm 33.5$  ms), as well as a shortening of the P wave ( $79.1 \pm 12.2$  ms vs.  $82.6 \pm 14.4$  ms) and PQ interval ( $146.4 \pm 19.6$  ms vs.  $148.3 \pm 20.1$  ms). Echocardiography confirmed left ventricular hypertrophy in 10.9% of the synthetic cathinones group and 17.1% of the opioid group. Transmitral left ventricular diastolic dysfunction was diagnosed in 23.5% of patients in both groups. Additionally, 31.1% of patients using synthetic cathinones and 44.1% of those using opioids had a reduced ejection fraction on echocardiography.

**Conclusion:** In patients using synthetic cathinones the QT interval was longer compared to those using opioids. The ejection fraction was lower in the opioid group. Electrocardiographic and echocardiographic screening should be conducted for all patients with post-acute withdrawal syndrome to prevent life-threatening arrhythmias and heart failure.

## KEYWORDS:

*Synthetic cathinones, opioids, cardiac symptoms, post-acute withdrawal syndrome*

## INTRODUCTION

New psychoactive substances (NPS) are a large group of recreational drugs, widely distributed under the guise of "legal" substances. NPSs are analogues of the main narcotic substances or a imitation of already existing psychoactive chemical compounds. Currently, more than 950 substances are known.<sup>1</sup> There is a growing interest in NPSs among young and adolescent drug users due to their availability, diversity and relative affordability. All this creates concerns in the health care system, in education, and in law enforcement agencies.<sup>2</sup>

Synthetic cathinones (SC) are one of the most prevalent and particularly popular chemical group among other NPSs. SC were first synthesized in 1928.<sup>3</sup> In the countries of Central Asia on the drug market SC appeared since 2015.<sup>4</sup> In these countries one of the most popular SCs are  $\alpha$ -pyrrolidinovalerophenone ( $\alpha$ -PVP) and 4-methylmethcathinone (mephedrone) according to the reports of law enforcement agencies. Clandestine laboratories illegally manufacturing  $\alpha$ -PVP and mephedrone are also a warning sign of the popularity of synthetic stimulants in the Central Asian region. For instance, Kazakhstan police reported about a manufacturing facilities that produced alpha-PVP and mephedrone for various territories of the country. Both alpha-PVP and mephedrone are listed as illegal drugs in Kazakhstan legal acts since the end of the 2010-s. Worldwide, these two substances were classified as hazardous drugs throughout more than a hundred countries and territories. Mephedrone was brought under Schedule II of the 1971 Convention on Psychotropic Substances at the 58th Commission on Narcotic Drugs (CND) in Vienna in 2015.<sup>5</sup> The following year, alpha-PVP was scheduled after the series of risk assessment by European Monitoring Centre for Drugs and Drugs Addiction and United Nations Office on Drugs and Crime.<sup>6</sup> Official documents notified a myriad of SC side effects and health risks.

Pharmacological profiles these SCs vary significantly.  $\alpha$ -PVP is a pyrovalerone derivative that exhibits strong dopamine transporter and norepinephrine transporter inhibition, but

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negligible serotonin transporter inhibition and negligible releasing properties.<sup>7</sup> Mephedrone is nonselective substrates for plasma membrane monoamine transporters, produces increases in extracellular dopamine and serotonin.<sup>8</sup> Due to these pathways indirect sympathomimetic effects entail a wide range of cardiovascular abnormalities.

Chest pain, tachycardia, hypertension are the main cardiac symptoms in those who use SC during the intoxication period.<sup>9,10</sup> Cases of myocardial infarction with ST segment elevation and multiple blood clots, atrial fibrillation, and cardiac arrest have been reported with alpha-PVP and mephedrone use.<sup>11-13</sup>

Opioids also remain the most commonly used illicit drugs in the Central Asia including Kazakhstan. Opioid using associated with cardiovascular disease and cardiovascular mortality.<sup>14</sup> With the advent of synthetic stimulants, opioids have not lost their relevance. Patients very often report poly-dependence with a combination of cathinones and opioids.<sup>15</sup>

Over the course of SC and opioid regular use, the period of withdrawal begins between 24 hours to 7 days following the last use of NPS.<sup>16</sup> During this period cardiac symptoms may be the same as in intoxication.<sup>17</sup> The post-acute withdrawal syndrome (PAWS) occurs after substance withdrawal and can last up to two months.<sup>17</sup> As of today, in our current knowledge, there has been no studies on the comparing chronic effects of SC and opioid on the cardiovascular system of patient with PAWS. This can cause difficulties in the clinician's understanding of the features of differential diagnosis. Therefore, this study describe and compare the clinical data of patients using SC and opioid with PAWS.

## MATERIALS AND METHODS

In our case-control design of study, over a period of six months, we examined 294 patients over 18 years of age who were hospitalized at the Mental Health Center for rehabilitation due to chronic dependence on NPS ( $\alpha$ -PVP and mephedrone) and opioid. We screened history cases for the presence of diagnostic code F15 (other stimulant related disorders) and F11 in ICD-10. In our study patients were included if they reported a history of SC and opioid use and those patients who indicated that more than 7 days had passed since their last substance use. Local Ethical Commission approval was obtained from Semey Medical University for conducting this study (Protocol No. 2 of 10/28/2020). All patients signed an informed consent form. Patients were excluded if they had clinical manifestations cardiovascular diseases (e.g., edema).

All patients underwent an express drug test (The NarcoCheck®) upon admission to the hospital. This test strip was made for the rapid detection in human urine of mephedrone and  $\alpha$ -PVP. This test was positive if the sample tested contains at least 500 nanograms of mephedrone and  $\alpha$ -PVP per milliliter of urine. The patients were also tested during hospitalization using an express test panel (morphine, tramadol).

Patients were asked about their use of all prohibited drugs (also about use of other sympathomimetic drugs, amphetamines, cocaine), mean duration of SC, opioid use, the maximum daily dose, and the way of drug administration. Data was collected on nicotine smoking, alcohol consumption, as well as complaints regarding the cardiovascular system.

For all patients, blood pressure (BP) was measured at the shoulder and ankle, and the ankle-shoulder index (ASI) was calculated. A cardiac auscultation was performed.

Indicators of the complete blood count and laboratory results of glucose, liver, kidneys function studies were obtained from the case histories. All patients underwent electrocardiography (ECG) on the Nihon Kohden Cardiofax S machine. ECG was interpreted by manual calculations. ECG was done by one investigator. All calculations of waves, intervals were carried out in milliseconds.<sup>18</sup> The sinus bradycardia was determined by heart rates below 60 beats per minute, and the sinus tachycardia by heart rates above 100 beats per minute. Early ventricular repolarization was diagnosed in the presence of concave ST segment elevation, notching at the point J, and asymmetric T waves on the ECG. It has been determined that left ventricular hypertrophy occurs when the Cornell index (R in avL + S in V3) is greater than 28 mm in men, and greater than 20 mm in women.

Transthoracic echocardiography (ECHO CG) was performed in all patients using the SonoScape SSI-6000. The measurements were taken in the parasternal and apical positions in millimeters. In the parasternal position the interventricular septum, the thickness of the posterior wall of the left ventricle (normal values: 6-10 mm), the end-diastolic (EDD) (normal values: 42-58.4 mm) and the end-systolic dimensions (ESD) (normal values: 25-39.8 mm), and aortic parameters were measured. PW and CW Doppler have been used to quantify blood flow velocity. Color Doppler was used to assess the nature of the blood flow. E/A ratio less than 0.8 confirms the existence diastolic dysfunction. The ejection fraction (normal values: >55%), end-diastolic (EDV) (normal values: 62-150 ml), end-systolic volumes (ESV) (normal values: 21-61 ml), stroke volume (SV) (normal range is 50 to 100 ml) of the left ventricle were assessed in the M-mode according to Teicholz. Right ventricular systolic function was assessed using fractional area change tricuspidannular plane systolic excursion (TAPSE normal values: >0.7cm).<sup>19</sup>

The IBM SPSS Statistics 20 program was used to perform descriptive analysis of quantitative and qualitative variables (percentage, mean M, and standard deviation SD). The t-test the Mann-Whitney U test were used to compare the quantitative data. The chi-square test was used to compare categorical data.

## RESULTS

Our study involved 183 patients using  $\alpha$ -PVP, mephedrone and 111 patients reporting opioid use. The average age of patients was 32.4±8.5 years. The male sex prevailed (87.4%) over the female (12.6%). 84.2% of patients used SC intranasally or by smoking, 71.2% used opioids

**Table I: Patient demographics, clinical characteristics and laboratory studies**

	SC users n=183	opioid users n=111	p
Age, average (SD)	29.3(6.2)	35.6(10.8)	<0.0001
Intranasally using or by smoking, n(%)	154(84.2)	-	<0.0001
Intravenously using, n(%)	27(14.8)	79(71.2)	<0.0001
using of tablets, n(%)	2(1)	32(28.8)	<0.0001
Maximum daily dose of the substance **, average (SD)	1.4(1.8)	12.7(6.6)	<0.05
Cardiac symptoms, n(%):	143(78.6)	49(44.1)	<0.0001
palpitations, n(%)	124(67.8)	28(25.2)	<0.0001
a feeling of lack of air, n(%)	83(45.4)	34(30.6)	<0.05
ALT, IU/L, average (SD)	40(81.9)	46.2(38.6)	<0.05
AST, IU/L, average (SD)	20.8(15.8)	42.8(45.2)	<0.0001

\*-years

\*\*-grams

ALT - alanine aminotransferase

AST - aspartate aminotransferase

**Table II: ECHOCG results**

	SC users n=183	opioid users n=111	p
The thickness of the posterior wall, mm, average (SD)	8.4(1.8)	9.2(2.1)	<0.05
Interventricular septum, mm, average (SD)	8.4(1.9)	9(2.1)	0.1
EDD, mm, average (SD)	43.9(8.3)	44.2(8.5)	<0.05
EDV, ml, average (SD)	89.3(34.7)	90.9(33.8)	<0.05
ESD, mm, average (SD)	28.6(7)	30.8(6.6)	0.7
ESV, ml, average (SD)	37.6(17.2)	39(18.1)	0.5
SV, ml, average (SD)	50.9(16.9)	51(17.7)	<0.05
E/A on TV, average (SD)	1.05(0.2)	1.02(0.2)	<0.05
E/A on MV, average (SD)	1.5(0.5)	1.4(0.5)	0.6
Ejection fraction for ECHO CG, %, average (SD)	58.8(7.8)	56.6(8.1)	<0.05
TAPSE, sm, average (SD)	2.4(0.3)	2.3(0.3)	<0.05

SD - standard deviation, SV - stroke volume, EDD - end-diastolic dimension, ESD - end- systolic dimension, EDV - end-diastolic volume, ESV - end- systolic volume, TV - tricuspid valve, MV - mitral valve, TAPSE - tricuspid annular plane systolic excursion.

intravenously. The last use of SCs was 1.2±1.3 months ago, opioids - 1.2±1.7. The average experience of SC uses was 3.9±3.5 years, opioid - 13.2±8.5. (Table I). Nicotine smoking among groups occurred in 92.5%. 19.7% of patients recovered from alcohol dependence.

65.5% of patients presented cardiac symptoms either during using and in withdrawal period. The leading symptoms were palpitations (51.7%) and a feeling of lack of air or shortness of breath (39.8%) (Table I). A stabbing type of pain was experienced in groups with SC (17.5%), 10.8% - with opioids. A pressing type of pain was experienced in 8.7% of cases with SC, 9% - with opioids. Patients reported that the duration of chest pain was observed to be between two and five minutes. The time of chest pain onset varied by substance with chest pain starting during only acute intoxication with alpha-PVP and only withdrawal syndrome with mephedrone. During the PAWS cardiac symptoms were fully resolved.

The average systolic blood pressure (SBP) on the arm in groups with SC was 124.1±11.8 mmHg, with opioid - 126.4±18.5 mmHg, diastolic blood pressure (DBP) with SC - 81.1±6.8 mmHg, opioid - 80.9±10.9 mmHg. On the leg, the SBP in first group was 143.6±19.4 mmHg, second - 143.9±21.9 mmHg and the DBP - 89.1±12.7 mmHg and 89.8±12.4 mmHg. The ASI was equal to 1.1±0.5 in SC group and

1.1±0.2, which corresponds to the limits of acceptable values. The number of heartbeats was equal to the pulse and 80±15.2 beats per minute were noted in both groups.

In the complete blood count, the indicators were within the reference range. The average blood glucose was 87.1 mg/dL±14.9, creatinine was 0.8 mg/dL±0.1, urea was 25.9 mg/dL±7.9. Laboratory results revealed an increase in the level of aspartate aminotransferase (AST) above 40 IU/L was noted in 18.0 % in group with SC, 30.6% - with opioids, and alanine aminotransferase (ALT) - 24.6% and 30.6% (value up to 40 IU/L was normal for our laboratory) (Table I).

In patients using SC, the ECG showed a lengthening of the average duration of the ventricular QRS complex (70.5±13.3 ms and 69.6±11.7 ms), T wave (154.1±27.5 ms and 140.4±24.1 ms), QT interval (338.2±28.5 ms and 334.8±33.5 ms), a shortening of the P wave (79.1±12.2 ms and 82.6±14.4 ms), PQ interval (146.4±19.6 ms and 148.3±20.1 ms). Sinus tachycardia was found in groups with SC in 3.8%, with opioid in 4.5%, bradycardia in 11% and 8.1%. Early ventricular repolarization syndrome was observed in groups with SC in 8.2 % of cases and with opioid in 6.3%. In 7.1% of cases there were signs of hypertrophy of the left ventricle in groups with SC, 9% - with opioids. Conduction disturbance in the form of a blockage of the right leg of the Gis beam was found in

14.8% in groups with SC, 13.5% - with opioids. Atrioventricular blockage of the I degree was found in one case in each group.

On ECHO CG left ventricular hypertrophy was confirmed in 10.9% in groups with SC, 17.1% - with opioids. Mitral regurgitation of the second degree occurred in 0.5% in first group, 2.7% in second group (0 and 1 degrees are acceptable values). Tricuspid regurgitation of the second degree occurred in 1.1% in groups with SC, 0.9% - with opioids. Transmittal left ventricular diastolic dysfunction was diagnosed in 23.5% in each group. 31.1% of patients on ECHOCG had a reduced ejection fraction in groups with SC, 44.1% - with opioids. Systolic function of the right ventricle was normal in both groups (Table II).

## DISCUSSION

To our knowledge this study provides for the first time an in-depth description and comparison of the clinical manifestations of the cardiovascular abnormalities in 294 patients who used SC and opioid with PAWS.

In our clinical study, male patients predominated, which does not contradict the data of other studies.<sup>20,21</sup> Our study found an average age of group SC users is 29.3±6.2 years, opioid users - 35.6±10.8 years, which corresponds average age of patients in other studies.<sup>20,21</sup>

Patients who use illicit drugs have CVD risk factor. Smoking nicotine is one of the leading risk factors for CVD.<sup>22</sup> In our study, 92.5% of participants reported regular smoking.

NPSs are found in the form of powders, tablets, capsules. Oral, intranasal (nasal inhalation) prevail, less often intramuscular / intravenous, rectal method of administration are used.<sup>23,24</sup> It is known that when smoking and inhaling, the effect occurs faster even with a small dose of NPSs.<sup>2</sup> In our study, the intranasal method for mephedrone and smoking for  $\alpha$ -PVP prevailed. Most often, the intravenous method is used by those who use heroin.<sup>23</sup> In our study the intravenous method and using of tablets dominate in the group of patients with opioids.

Tachycardia and hypertension are the main cardiac effects of SC use. While one of the symptoms of opioid withdrawal syndrome is tachycardia.<sup>25</sup> According to our ECG study, sinus tachycardia and bradycardia were detected in 3.8% and 11% in group with SC, with opioid in 4.5% and 8.1% of subjects, respectively. Probably bradycardia was associated with the absence of a period of SC and opioid intoxication.

QT interval was matters of great importance because of the relationship between prolongation of this and lethal ventricular arrhythmias.<sup>18,25</sup> Prolongation of the QT interval with the development of life-threatening arrhythmias on the ECG may be a consequence of the direct toxic effect of SC on cardiomyocytes.<sup>26,27</sup> To the best of our knowledge, there has been no studies on the chronic effects of  $\alpha$ -PVP and mephedrone on ECG alterations of patient with PAWS. A study of B. Ünübol with 90 patients experienced opioid withdrawal and PAWS revealed QT interval prolongation. In contrast, our study discovered higher QT value in patients with SC, which was shorter than normal limits.<sup>18</sup>

Remodeling of the left ventricle can occur, as a result, of the sympathomimetic effect of SC with prolonged and continuous use.<sup>28</sup> There is no probable evidence of the effect of opioids on left ventricular remodeling.<sup>29</sup> In our small observation, we diagnosed hypertrophy of the left ventricle on the ECHO CG in 10.9% in groups with SC, 17.1% - with opioids. A study of M. Selcuk with 85 individuals, where 45 patients smoking heroin, experienced an increase in right ventricular diameter in the opioid group.<sup>29</sup> In our study there are no differences in the diameter of the heart chambers.

The first study of the effect of mephedrone on the heart muscle in 2012 experienced an the development of myocardial ischemia associated with cardiac arrest with high contractility.<sup>24</sup> Although heroin use does not have any effect on left ventricular function,<sup>29</sup> according to the our study 31.1% of patients had a situation between normal and reduced ejection fraction in groups with SC, 44.1% - with opioids. To the best of our knowledge, there has been no studies of left ventricular diastolic function in patients using SC. Left ventricular diastolic dysfunction was diagnosed by us in 23.5% in each group.

To our knowledge, this is the first description of clinical cardiac manifestations on the example of a case-control design study of chronic use of SC and opioid in the post withdrawal period. The description of the cases of chronic use of SC and opioids in the post withdrawal period partially demonstrates clinical manifestations of the cardiovascular abnormalities. Limitations of the work include the difficulties in laboratory identification cases of NPS and opioid use, the lack of quantitative confirmation, and the chaotic use of psychoactive substances limits the identification of specific cardiac signs related to stimulants. This clinical symptom registration was retrospective, and there is a high level of reproduction error. The study did not account for the corrected QT interval on the ECG. Left ventricular ejection fraction was assessed only by the Teicholz method, and right ventricular ejection fraction - only by TAPSE. Ventricular diastolic function has not been assessed by other methods, such as tissue Doppler.

## CONCLUSION

Withdrawal syndrome from synthetic cathinones is linked to a prolonged QT interval on the ECG, in contrast to opioid withdrawal, highlighting the importance of regular QT interval monitoring to prevent serious arrhythmias. Conversely, opioid withdrawal is associated with a more pronounced reduction in left ventricular ejection fraction compared to synthetic cathinones. This suggests the need for evaluating natriuretic peptides in opioid withdrawal patients and considering treatments for chronic heart failure with preserved ejection fraction.

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