ABSTRACT

of the PhD dissertation by Ainur Maratovna Shukimbayeva entitled "Cardiovascular Pathology in Patients Abusing New Psychoactive Substances," submitted in fulfillment of the requirements for the degree of Doctor of Philosophy (PhD) in the specialty 8D10102 - "Medicine."

Background and Rationale of the Study. New psychoactive substances (NPS) - commonly referred to as "designer drugs" - are synthetic analogues of established psychoactive compounds that have been chemically modified to circumvent international control [UNODC, 2023]. While these substances mimic the effects of amphetamines, opioids, cannabinoids, and cathinones, they possess significantly higher toxicity and unpredictable pharmacodynamic properties [Luethi D., Liechti M.E., 2020]. The primary mechanism of their action involves the activation of the dopaminergic, serotonergic, and noradrenergic systems, leading to potent stimulation of sympathetic activity manifested by tachycardia, hypertension, and vasospasm. Furthermore, NPS-induced mitochondrial dysfunction and oxidative stress result in myocardial damage, QT interval prolongation, and the risk of fatal arrhythmias [Kurcevič E. et al., 2020].

Despite their growing prevalence and clinical significance, the cardiotoxic effects of NPS remain insufficiently understood. Available data primarily address acute intoxications [Luethi D. et al., 2022], whereas the state of the cardiovascular system during withdrawal and post-withdrawal periods remains extremely poorly documented. This creates a gap in understanding the reversibility and chronicity of myocardial injuries, thereby hindering early diagnosis and the prevention of complications. Consequently, conducting a comprehensive clinical and instrumental study aimed at identifying the specific characteristics of cardiovascular disorders in individuals abusing NPS is of profound scientific and practical value.

Aim of the Study

To identify clinical and diagnostic predictors of cardiovascular involvement in individuals abusing new psychoactive substances.

Research Objectives

1. To investigate the pattern of cardiovascular disorders in patients abusing NPS, depending on the period, duration of substance use, and the level of tolerance to NPS.
2. To perform a comparative analysis of the effects of NPS versus classical psychoactive substances (opioids) on the functional state of the cardiovascular system in drug users during the intoxication, withdrawal, and post-withdrawal periods.
3. To develop an algorithm for the early diagnosis of cardiovascular complications in individuals abusing NPS, based on the identified clinical and diagnostic predictors.

Study Design: A combined retrospective-prospective, multicenter, comparative-descriptive study.

Inclusion Criteria:

- individuals aged 18 years and older;

- admission for inpatient substance use treatment between January 1, 2021, and December 31, 2022;
- a documented history of new psychoactive substance (NPS) use (one or more times);
- informed consent to participate in the study.

Exclusion Criteria:

- age under 18 years;
- conditions impairing the capacity to provide informed consent (e.g., psychosis, intellectual disability, dementia).

Endpoints: all-cause mortality.

Materials and Methods

To address the first objective, 566 medical records from the 2015–2020 period were retrieved from the archive of the Pavlodar Branch of the Republican Scientific and Practical Center for Mental Health (PB RPCMH). The study included case records of patients with opioid dependence, as well as dependence on NPS and tropicamide. Data extraction into a dedicated EXCEL research spreadsheet was performed, capturing parameters such as age, sex, types of substances used (primary and secondary), dosages, duration of substance use, time since last use, cardiovascular risk factors, laboratory findings, electrocardiography (ECG) data, and comorbidities.

To address the second objective, a cardiovascular study was conducted during the acute intoxication period at the Multidisciplinary City Hospital No. 1 in Astana. The study involved 21 patients with new psychoactive substance (NPS) poisoning and 11 patients with opioid poisoning. Upon admission, all patients underwent rapid screening: a NarcoCheck® rapid test for mephedrone and α-PVP, as well as an enzyme-linked immunosorbent assay (ELISA) rapid test to detect MOP, THC, TRA, EDDP, BZO, MDPV, and synthetic cannabinoids (SC). Clinical and diagnostic methods included the evaluation of cardiospecific biomarkers (Troponin-I test, LLC "HAN MEDTEST"; De Ritis ratio, calculated as the aspartate aminotransferase to alanine aminotransferase [AST/ALT] ratio), electrocardiography (ECG), and echocardiography (EchoCG).

The study of the cardiovascular system in patients abusing NPS during the withdrawal and post-withdrawal periods was conducted at the Pavlodar Branch of the Republican Scientific and Practical Center for Mental Health and the City Center for Mental Health in Astana. A total of 341 patients in the withdrawal and post-withdrawal periods were examined. In this study, the withdrawal period was defined as a time interval of 1 to 10 days after the last use of the psychoactive substance, during which patients exhibited pronounced autonomic, psychoemotional, and somatic manifestations of the withdrawal syndrome. The post-withdrawal period included patients within an interval of 11 days to 6 months after cessation of use, characterized by the regression of acute intoxication symptoms and the stabilization of their somatic condition. Special attention was paid to the specific patterns of NPS use, namely the duration of "binge" periods (when drug-dependent individuals continuously used NPS from several days up to a month).

Two years after the initial examination, the vital status of the patients was assessed by cross-referencing their data with the Electronic Registry of Disciplinary Patients. Verification of all-cause mortality was performed based on official medical documentation and registration records.

Statistical data analysis was performed using IBM SPSS Statistics 27 software. The normality of quantitative variable distribution was pre-assessed using the Shapiro–Wilk test. For normally distributed data, intergroup differences were evaluated using Student's t-test for independent samples. In cases of non-normal distribution, the non-parametric Mann–Whitney U test was applied. The Kruskal–Wallis test was used to assess differences among three or more samples. Qualitative (categorical) data were analyzed using Pearson's chi-squared test. For binary variables, the prevalence odds ratio (OR) and its 95% confidence interval (CI) were additionally calculated

To evaluate the contribution of various clinical, laboratory, and sociodemographic characteristics to the development of myocardial electrophysiological activity disorders and systolic dysfunction, a linear regression analysis was performed.

To evaluate the dependence of the binary variable "mortality" on a combination of quantitative and qualitative factors, a binary logistic regression model was constructed.

To eliminate the confounding effect on the association between the factor and the outcome, propensity score matching (PSM) was utilized.

Key Statements for the Defense:

1. Patients who abuse NPS exhibit signs of cardiovascular damage characterized by hypertension, arrhythmias, and cardiotoxicity at all stages of substance use; the severity of these manifestations is determined by the duration of substance use, tolerance levels, and "binge" patterns.

2. Patients who abuse NPS are characterized by acute electrophysiological changes, whereas those who abuse opioids exhibit chronic structural and functional disorders; furthermore, NPS use was established to be associated with higher mortality rates compared to opioid dependence.

3. The developed algorithm enables early diagnostic screening for adverse cardiac complications within the NPS group and facilitates the identification of initial manifestations of cardiotoxicity based on key predictors of cardiovascular events.

Scientific Novelty

1. For the first time in Kazakhstan, comprehensive data have been obtained on the structure of cardiovascular disorders among NPS users across various stages of substance use.

2. For the first time, distinct differences in the structure and frequency of cardiovascular disorders have been established between NPS users and patients with opioid dependence.

3. For the first time, utilizing rapid screening test systems, a distinct clinical profile of the NPS-abusing patient was established, encompassing characteristic clinical, laboratory, and cardiovascular alterations.

4. For the first time, all-cause mortality risks attributable to the cardiotoxic effects of NPS and opioids were evaluated and differentiated according to their specific impact profiles.

5. For the first time, an algorithm for the early diagnosis of cardiovascular complications in NPS-abusing individuals has been developed and validated, enabling the timely identification of early signs of cardiotoxic effects.

Practical Significance

1. Data obtained on the pattern of cardiovascular disorders in NPS-abusing individuals enhance the effectiveness of early detection of cardiotoxic complications in the clinical practice of cardiologists, psychiatrists-addictologists, toxicologists, and emergency medicine specialists (Implementation Certificate).

2. Identified differences in the structure of cardiovascular disorders between NPS users and patients with opioid dependence allow for a differentiated approach to the diagnosis, monitoring, and risk assessment of adverse outcomes in substance users (Authorship Certificate No. 38655).

3. A clinical profile of the NPS-abusing patients with novel psychoactive substance (NPS) abuse was developed and implemented as methodological recommendations for practical application in healthcare settings (Authorship Certificate No. 72187).

4. Methodological recommendations and an algorithm for the early diagnosis of cardiovascular disorders in NPS-abusing patients have been developed and formalized (Authorship Certificate No. 63199).

Conclusions:

1. Cardiovascular disorders in NPS-abusing individuals are characterized by arrhythmic, hypertensive, and cardiotoxic patterns and are observed across all stages of substance use. The severity of pathological alterations depends on the duration of substance use, tolerance levels (median 3 (3.5) years with a daily dose of 0.5 (1.5) g), and the frequency of "binge" episodes.

2. A comparative analysis of the studied groups revealed the following differences:

- the NPS group was characterized by electrophysiological (QTc prolongation in 8.1%), hemodynamic (blood pressure 130 (5) mmHg), and cardiotoxic (an increase in the de Ritis ratio to 1.7 (0.5)) disorders;
- opioid-dependent users showed a predominance of chronic structural and functional alterations, including reduced myocardial contractility (LVEF 49 (9)%), dilation of cardiac cavities, and pulmonary hypertension (33 (12.2) mmHg).
- the mortality rate was significantly higher in the NPS group compared to the opioid group (31.3% and 8.9%, respectively; $p < 0.01$).

3. Based on the identified predictors of life-threatening conditions (QTc $\ge$ 415 ms, "binge" use exceeding 7 days), an algorithm for the early diagnosis of cardiovascular complications in NPS-abusing individuals was developed, enabling the timely verification of fatal arrhythmia risks.

Approbation of the Research Work

The core results of the dissertation research were presented and discussed at the XV International Scientific and Practical Conference "Ecology. Radiation. Health," dedicated to the 30th anniversary of the closure of the Semipalatinsk Test Site (Semey, August 2021); the VIII International Conference on Novel Psychoactive Substances in Washington (November 2021); the II International Scientific and Practical Conference "Modern Pharmacy: New Approaches in Education and Current Research," timed to the 20th anniversary of the Faculty of Pharmacy (Nur-Sultan, May 2022); the IX International Conference on Novel Psychoactive Substances (NPS) in Panama (October 2022); and the VI Scientific and Practical Conference of the Ural Federal District, dedicated to the 50th anniversary of the Acute Poisoning Treatment Service of the Sverdlovsk Region (November 2023).

Publications

A total of 7 scientific works have been published on the topic of the dissertation, including 1 methodological recommendation and 4 articles. Among the articles, 3 were published in peer-reviewed journals recommended by the Committee for Control in the Sphere of Education and Science, and 1 article was published in the Medical Journal of Malaysia (indexed in the Scopus and Web of Science international databases, Q3 quartile). Additionally, 3 conference abstracts were published, which involved a poster presentation at the VIII International Conference on Novel Psychoactive Substances in Washington, an online presentation at the IX International Conference on Novel Psychoactive Substances (NPS) in Panama, and a presentation at the VI Scientific and Practical Conference of the Ural Federal District, dedicated to the 50th anniversary of the Acute Poisoning Treatment Service of the Sverdlovsk Region. Furthermore, 3 Authorship Certificates (No. 38655, No. 63199 and No72187) have been obtained.