https://doi.org/10.31925/farmacia.2023.1.3 **ORIGINAL ARTICLE**

CHARACTERIZATION OF VARIOUS GROUPS OF DRUGS USERS. HIGHLIGHTS ON LEGAL HIGHS USERS

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Manuscript received: October 2022

Abstract

Our article aimed to assess the differences among various drug users' groups, especially from haematological, biochemical, urinary and cardiological perspectives. A retrospective study was conducted in collaboration with C.E.T.T.T. "Sfântul Stelian" detoxification centre, in Bucharest, Romania. The medical records of 2572 hospitalized patients, between 2015 and 2021, were analysed. The study group was characterized taking into account demographic data, personal history/co-morbidities, history of consumption and substitution treatment. Clinical/paraclinical evaluations were performed. The outcome of the study outlined that GGT (gamma-glutamyltransferase) might be correlated with both alcohol intake and the presence of contagious diseases, a decrease of MCH (mean corpuscular haemoglobin) and MCHC (mean corpuscular haemoglobin concentration) homogeneously characterizes the entire study group, while the occurrence of particular cardiological events might be correlated with certain substances group. Overall, the study provides information on the different types of consumers, but also supports future research on correlating the variable parameters with the possible chemical structures of the consumed compounds detected.

Rezumat

Studiul și-a propus să evalueze diferențele dintre grupuri variate de consumatori de droguri, în special din punct de vedere hematologic, biochimic, urinar și cardiologic. S-a desfășurat un studiu retrospectiv în colaborare cu centrul de dezintoxicare „Sfântul Stelian" din București. Au fost analizate foile de observație ale 2572 pacienți spitalizați între 2015 și 2021. Pentru grupul de studiu au fost caracterizate datele demografice, istoricul personal/comorbiditățile, istoricul de consum și tratament de substituție; au fost efectuate și evaluări clinice/paraclinice. Rezultatul studiului a evidențiat faptul că GGT (gamma-glutamiltransferaza) ar putea fi corelată atât cu consumul de alcool, cât și cu prezența bolilor contagioase, iar o scădere a MCH (hemoglobină eritrocitară medie) și MCHC (concentrația hemoglobinei eritrocitare medie) caracterizează în mod omogen întregul grup de studiu, în timp ce apariția unor evenimente cardiologice particulare ar putea fi corelată cu anumite grupe de substanțe. În ansamblu, studiul oferă informații despre diferitele tipuri de consumatori, dar susține și cercetările viitoare privind corelarea parametrilor variabili cu posibilele structuri chimice ale compușilor consumați detectați.

Keywords: alcohol, Cannabis, cardiac, haematological and biochemical parameters, opiates

Introduction

Due to multiple pieces of research in recent decades, the mechanism of toxicity is now well-known for most addictive substances. Moreover, rapid analysis methods have been developed for urine detection, including opiates, benzodiazepines (BZD), methadone, cannabis, ecstasy and/or cocaine. The advantage of urine drug testing, over other drug tests, is its rapidity and simplicity of use. Unfortunately, this method can lead to false-positive results and need to be confirmed by performant methods [1, 2]. Unfortunately, for the New Psychoactive Substances (NPS) there is no such rapid analysis method available.

New Psychoactive Substances (NPS) represent a complex group of substances of abuse that have lately flooded the drug market and were designed to mimic illicit drugs and their psychoactive effects. Being

structurally different, these drugs were intended to escape legislative control. NPS includes defined groups of drugs as follows: synthetic cannabinoids [3-7], cathinone [8, 9], phenethylamines [10, 11], piperazines [12], plant-based substances, hallucinogens [12, 13], synthetic opioids and synthetic benzodiazepines. NPS are known, by the general population, as "legal highs", "research chemicals" and "designer drugs", because tend to be analogs of existing controlled drugs [14, 15].

Given the fact that many drug users combine various substances, they often develop unspecific symptoms, making it difficult for specialists to accurately identify the incriminated substance [16]. Although each class of drug has certain peculiarities, due to poly-consumption or the use of new psychoactive substances (NPS), it is rarely possible to conclude the type of drug that caused the intoxication based only on clinical examination.

More than that, due to the action on multiple systems, the clinical picture of patients consuming various substances of abuse is usually similar [16].

Due to the impact of drug abuse on the cardio-vascular system, some information regarding the changes that may appear on a normal electrocardiogram (ECG) is to be outlined [17, 18]. Sometimes, the changes that occur on the electrocardiogram can be indications of some pathologies of major clinical significance. However, due to the use of certain substances (such as amphetamines, benzodiazepines, xanthines, lithium, etc.), electrolyte imbalances, muscle manifestations such as chills (due to hypothermia, fever, or chills in withdrawal), or if patients move during the test, ECG artifacts [19], baseline irregularities, waveform interferences (P-wave, QRS-complex, or T-wave changes) [20], or ventricular [15] and supra-ventricular arrhythmias may occur [21-25]. The main pathological changes that may appear in ECG and their causes are listed in Table I below.

Regarding the changes in the biochemical parameters, GGT (gamma-glutamyltransferase) usually increases in case of alcohol abuse as GGT is a well-known biomarker for heavy alcohol intake. Studies have outlined a correlation with heroin addicts as well [26-29].

Table I

Main pathological changes in the electrocardiogram and their causes

Pathological change	Causes/association with pathology [reference]
Right branch block	Heart diseases such as myocardial infarction, heart failure, or various heart blocks [23]
Left bundle branch block	Myocardial injury or hypertrophy, hypertension, acute coronary synchromesh, chronic myocardial infarction, mitral and aortic valve disease [18, 25]
Aberrant ventricular complex	Myocardial infarction [15, 20]
Bradycardia	Inherent aetiology (ischemic heart disease, pericarditis, coronary artery disease), extrinsic causes (such as the administration of beta-blockers, narcotics and cannabinoids) [22]
Tachycardia	Physiological factors (sinus tachycardia), pathological factors (heart disease such as myocardial infarction, acute ischemic coronary heart disease, heart failure), and can also be induced by withdrawal [21, 24]
Atrial flutter	Risk factors such as old age, hypertension and a history of alcohol abuse [17]

In this regard, we conducted a retrospective study on a group of patients addicted to various classes of substances of abuse, hospitalized at the C.E.T.T.T (Toxic Addiction Assessment and Treatment Centre for Young People) "St. Stelian" detoxification centre in Bucharest, Romania. Among the above-mentioned NPS, the study at the centre included information about synthetic cannabinoids and cathinone users only. The main objective of the study was to highlight the main characteristics of different classes of drug users.

Materials and Methods

The study group consisted of 2572 drug users, addicts and patients hospitalized for either detoxification or inclusion in the methadone maintenance program or treatment of an acute abuse drug consumption episode. Their medical data were collected by accessing the detoxification centre's archive, through a retrospective study, for a period of 6 years (between January 2015 and January 2021). The study was approved by the Ethics Commission of the centre.

The study group was characterized in detail, taking into account demographic data, personal history/co-morbidities, history of consumption, history of methadone maintenance treatment (MMT) and clinical and paraclinical evaluation. Cardiological examinations were included for some patients at the decision of the attending physician.

The indicators/parameters followed were: age, sex, history of use of certain substances (details on the age of onset of substance use, association with other substances), history of treatment (patients with a history of MMT, age at the onset, methadone maintenance dose, drug dose at the onset), cardiological examination, urinary toxicological examination, urine summary and haematological tests (to assess changes in various parameters, both haematological and biochemical, in the context of drug use). It is worth to mention that COVID-19 pandemic has influenced the dynamics of drug market and users.

Statistical analysis

The collected data were assessed using the Chi-square test of independence. A p value < 0.05 was

considered statistically significant. For situations where only two categories of drugs of abuse consumers were compared, the Yates correction was applied.

Results and Discussion

The results obtained from the study group, including 2572 patients, women and men, aged between 16 and 71 years, are presented in Table II.

Table II

Characterization of the study group

Parameter	Group characteristics		
Sex	Males: 2283 (88.76 %) Females: 289 (11.24%)		
Substance of abuse	Opiates: 1304 (50.70%); Legal highs: 199 (7.74%); Alcohol: 107 (4.16%); BZD: 70 (2.72%); Cannabis: 99 (3.85%); Multiple drugs: 752 (29.24%); Other: 41 (1.59%)		
Male/female ratio	7.89		
Male/female (ratio depending on the drug of abuse)	Opiates: 9.51; Legal highs: 6.65; Alcohol: 14.28; BZD: 3.66; Cannabis: 3.12; Multiple drugs: 7.44; Other: 9.25.		
Age (years) (mean ± SD)	Male: 31.67 ± 6.83 (min 16, max 71) Female: 31.65 ± 6.83 (min 16, max 49)		
Age at the onset (years) (mean ± SD)	Mean 19.61 ± 6.14 (min 8; max 48)		
	Legal highs: 19.69 ± 6.15; Opiates: 19.63 ± 6.14; Cannabis: 19.70 ± 6.14; Multiple drugs: 19.71 ± 6.14; Other*: 19.37 ± 5.85.		
Age range/categories	< 18 years: 2 (0.07%); 18 - 22 years: 248 (9.64%); 23 - 27 years: 407 (15.82%); 28 - 32 years: 792 (30.79%); 33 - 37 years: 687 (26.71%); 38 - 42 years: 318 (12.36%); 43 - 47 years: 53 (2.06%); 48 - 52 years: 38 (1.47%); 53 - 57 years: 10 (0.38%); 58 - 62 years: 7 (0.27%); > 63 years: 5 (0.19%)		
History of (MMT) - male:female ratio	87.99% male; 12.01% female 7.32		
Daily methadone dose during MMT (mg) (mean ± SD)	72.96 ± 31.74 (min 10; max 160)		
Daily drug dose (balls/sachets/ joints) (mean ± SD)	Heroin: 4.62 ± 3.37; Legal highs: 4.04 ± 3.68; Cannabis: 1.08 ± 0.31. *1 "ball" = approx. 0.33 g*		
Policonsumption	Total users 752 (29.24%)	Males	Females
	Legal highs: Heroin: Cannabis: Alcohol: BZD:	188/2572 (7.31%) 284/2557 11.04%) 110/2572 (4.28%) 45/2572 (1.7%) 102/2572 (3.97%)	21/2572 (8.13%) 32/2572 (1.24%) 16/2572 (0.62%) 6/2572 (0.23%) 18/2572 (0.7%)
Singular use	Total users 1820 (70.76%)	Males	Females
	Opiates: Legal highs: Alcohol: BZD: Cannabis: Other:	1180/2572(50.70%) 173/2572 (6.73%) 100/2572 (3.89%) 55/2572 (2.14%) 75/2572 (2.92%) 37/2572 (1.44%)	124/2572 (4.82%) 26/2572 (1.01%) 7/2572 (0.27%) 15/2572 (0.58%) 24/2572 (0.93%) 4/2572 (0.16%)
Cardiological examination (number of patients)	Total 584 (22.70%) (265 – without changes, 319 – with changes)		
	Legal highs: 60 (10.27%); Opiates: 266 (45.55%); Cannabis: 27 (4.62%); BZD: 16 (2.74%); Alcohol: 24 (4.11%); Other: 4 (0.68%); Multiple drugs: 187 (32.02%)		
Cardiological changes	Total patients with at least one change – 319 *Total changes – 701*		
	Infarction: 63/701 (8.99%); Abnormal ECG: 204/701 (29.10%); Hypertrophy: 51/701 (7.28%); Bradycardia: 25/701 (3.57%); Tachycardia: 24/701 (3.42%); Axis deviation: 74/701 (10.56%); Aberrant ventricular complex: 37/701 (5.28%); Branch block: 104/701 (14.84%); Atrial fibrillation: 13/701 (1.85%); Supraventricular rhythm: 21/701 (3%); P wave: 36/701 (5.14%); Increased QT interval: 20/701 (2.85%); ST elevation: 12/701 (1.71%); Atrial conduction defect: 14/701 (2%); Atrial flutter: 3/701 (0.43%).		
Urinary examination (number of patients)	Total patients 268 (10.42%)		
	Pathological changes 183 (68.28%): Parameter (reference values): number of cases (%)		
	Albumin (< 10 mg/dL): 50 (27.32%); Urobilinogen: (negative, mg/dL): 103 (56.28%); Bile pigments (negative, mg/dL): 75 (40.98%); pH (4.8 - 7.4): 6 (3.28%); Ketone bodies (negative, mg/dL): 10 (5.46%); Leukocytes (negative, /μL): 7 (3.83%); Nitrites (negative): 4 (2.19%); Red blood cells (negative, /μL): 2 (1.09%)		

Parameter	Group characteristics
Urinary parameters (mean ± SD)	Albumin (< 10 mg/dL): 31.4 ± 9.90; Urobilinogen (negative, mg/dL): 2.85 ± 1.39; Bile pigments (negative, mg/dL): 1.6 ± 0.81
Haematological and biochemical examination (number of patients)	Total examinations: 631 (24.53%)
	Total examinations with pathological changes: 506 (87.63%)
	Legal highs: 61/506 (12.05%); Cannabis: 26/506 (5.13%); Opiates: 193/506 (38.14%); BZD: 24/506 (4.74%); Alcohol: 19/506 (3.75%); Other: 5/506 (0.98%); Multiple drugs: 178/506 (35.17%).
Haematological and biochemical changes:	Parameter
	ESR: 9↑, 92↓; LYM: 1↓, 151↑; GGT: 97↑; TGO: 112↑; TGP: 114↑; Cholesterol: 89↓, 23↑; Triglycerides: 4↓, 81↓; MCH: 268↑, 3↓; MCHC: 253↓, 2↑; Blood glucose: 15↑, 3↓; Urea: 24↓; Uric acid: 9↓, 31↑
Comorbidities (HVC, HVB, HIV)	Total 730 patients (28.38%)
	Cannabis: 5/730 (0.68%); Legal highs: 33/730 (4.52%); Opiates: 479/730 (65.61%); Alcohol: 8/730 (1.09%); BZD: 10/730 (1.37%); Multiple drugs: 195/730 (26.71%)

↑ = number of cases with increased values; ↓ = number of cases with decreased values; Methadone maintenance treatment = MMT; *Other drugs: cocaine, amphetamine, ecstasy, inhalants; Reference values: ESR (erythrocyte sedimentation rate) (6 - 11 mm/h); LYM (lymphocytes) (20 - 40%); GGT (Gamma-glutamyltransferase) (2 - 49 IU/L); TGO (oxaloacetic glutamic transaminase) (2 - 38 IU/L); TGP (glutamate-pyruvate transaminase) (2 - 41 IU/L); Cholesterol [150 - 240 mg%); Triglycerides (40 - 140 mg%); MCH (mean corpuscular haemoglobin) (25 - 32 pg); MCHC (mean corpuscular haemoglobin concentration) (28 - 36 g/dL); Blood glucose (55 - 115 mg/dL); Urea (15 - 45 mg%); Uric acid (3 - 6 mg%)

Demographic characteristics

To characterize the group from a demographic point of view, the following aspects were taken into account: age at the time of admission, age at the onset of consumption (where information was available), the age distribution of consumers according to the substance consumed and sex.

Indicator: age and sex. Out of the total of 2572 patients, included in the study, the majority were men (2283) and a small part were women (289), the ratio of men/women being 7.89. The distribution of patients by sex was also done in the context of the consumption of certain categories of drugs (Figure 1).

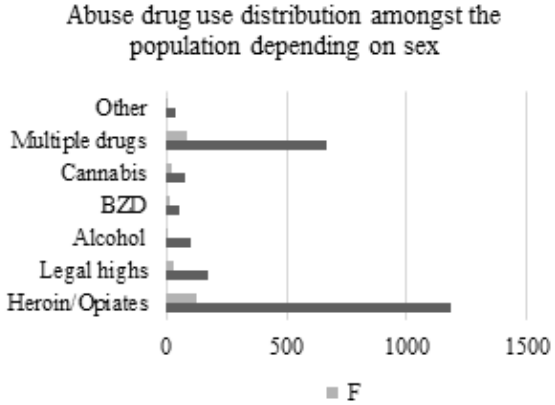

Figure 1.
Abuse drug use distribution amongst the population depending on sex

The mean age of the patients included in the study is 31.66 ± 5.65 years and ranges from 16 to 71 years (Figure 2). For males, the mean age is 31.67 ± 6.83 years and ranges from 16 to 71 years, while for females the mean age is 31.65 ± 6.83 years with a variation between 16 and 49 years.

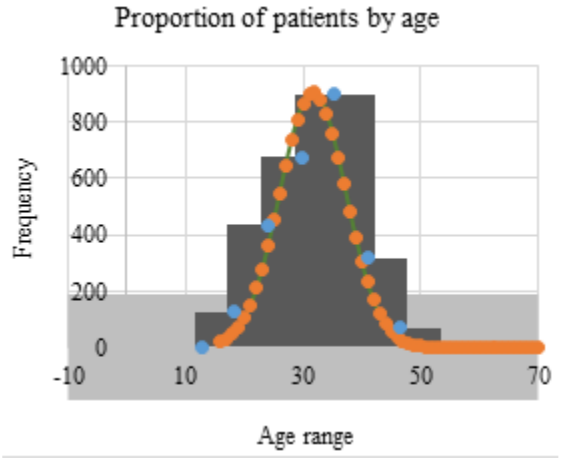

Figure 2.
The proportion of patients by age

Indicator: age at the onset and sex. The mean age at the onset is 19.61 ± 6.14 years (min 8 years; max 48 years), almost similar for the investigated groups of consumers (Table II). Data regarding the age at the onset of consumption were collected for 565 patients. Of these, a total of 72 patients started their addiction by using legal highs (representing 12.74%), 59 cannabis (10.44%), 411 heroin (72.74%), 16 started with more than one substance (2.83%) and 7 patients started with substances such as cocaine, amphetamine, ecstasy, inhalants or methadone pills (1.23%).

The minimum age at the onset of consumption reported to the type of substance of abuse is as follows: 11 years for legal highs, 10 years for cannabis, 10 years or heroin, 12 for polyconsumption and 8 for others (inhalants).

Indicator: type of substance of abuse

To characterize drug use in the study, subgroups of different drug users were analysed, either in single-

use or policonsumption, and where possible, the average daily dose was calculated.

Legal highs. Among legal highs users, the situation is almost similar in terms of single consumption (a total of 199 patients of both sexes – 173 men and 26 women *vs*. associated use (a total of 209 patients of both sexes – 188 men and 21 women). The majority of patients declared that they most frequently consumed legal highs known by their street names as "Pur", "Magic White" and "Spice". In the case of the combination with other drugs, the majority of patients associated legal highs with opiates (a total of 148 patients, of which 88.51% were men and 11.48% women), 30 patients associated legal highs with cannabis (of which 93.33% were men and 6.66% women), 17 patients associated more than 3 classes of substances (all were male) and only a few associated legal highs with drugs such as cocaine (2 men), benzodiazepines (3 men), alcohol (6 men and one woman) and inhalants (2 men). Regarding the dose, the average daily dose is 4.04 ± 3.68 sachets (3.35 ± 2.61 for women and 4.01 ± 3.71 for men) with a minimum of 1 sachet/day and a maximum of 20 sachets per day.

Opiates. Among opiates users (including heroin), there is a majority of consumers who prefer single-use (a total of 1304 patients of both sexes – 1180 men and 124 women) vs. combined consumption (a total of 316 patients – of which 284 men and 32 women). In the case of the combination of opiates with other drugs, most consumers preferred the association with legal highs (a total of 145 patients – of which 128 were men and 17 were women), followed by the association with benzodiazepines (a total of 63 patients – 57 men and 6 women) and cannabis (41 patients – 38 men and 3 women). Users also reported the association of opiates with more than 3 classes of substances (total 39 – 33 men and 6 women), 19 patients associated opiates with alcohol (16 men and 3 women) and only 9, all males, associated opiates with cocaine. Heroin is usually sold in small plastic packages that take a round shape similar to a ball, a one dose of heroin being therefore known by the users as a "ball". According to the users, from 1 gram of heroin 3 small balls are obtained (1 ball represents approx.. 0.33 grams). Regarding the daily dose, the average daily dose is 4.62 ± 3.37 balls/day (4.66 ± 3.40 balls/day for women and 4.62 ± 3.37 balls/day for men) with a minimum of 1 ball/day and a maximum of 12 balls/day for women and 20 balls/day for men.

Cannabis. Among cannabis users, the majority of users preferred combined consumption (a total of 126 patients of both sexes, of which 110 men and 16 women) *vs.* single consumption (a total of 99 patients of both sexes – 75 men and 24 women). In the case of the association of cannabis with other substances of abuse, similar results were outlined for both association with various opiates, of which heroin predominates (a total of 32 patients – 29 men and 3 women) and legal highs (a total of 31 patients, of which 29 male and 2 female). Additionally, almost similar results were obtained regarding the association of cannabis with more than 3 classes of drugs (a total of 29 patients, 23 men and 6 women). Regarding the association of cannabis with benzodiazepines, 24 patients were identified (17 men and 7 women). To a lesser extent, associations with alcohol (4 men), cocaine (3 men), ketamine, LSD (2 men) and inhalants (1 man and a woman) were outlined. Regarding the daily dose, the average daily dose is 1.08 ± 0.31 g/day, with a minimum of 0.5 g/day and a maximum of 2 g/day.

Alcohol. Among alcohol users, there is a majority of consumers who preferred single alcohol consumption (a total of 107 patients – 100 men and 7 women) and only 32.27% of patients included in the study associated alcohol with other substances of abuse (a total of 51 patients, of which 45 men and 6 women). In the case of the combination of alcohol with other substances of abuse, predominates the use of heroin or other opiates (17 patients – 14 men and 3 women), 11 patients associated alcohol with benzodiazepines (9 being men and 2 women), 10 patients consumed more than 3 classes of substances of abuse in addition to alcohol use (all males), 7 patients combined alcohol with NSP (6 men and one woman), 4 male patients combined it with cannabis and 2 men combined alcohol with antidepressants and gambling addictions.

Benzodiazepines. Among benzodiazepine users, the majority of patients combined benzodiazepines with other substances of abuse (a total of 120 patients of both sexes – 102 male and 18 female) and only 36.84% used benzodiazepines without other combinations (a total of 70 patients of both sexes – 55 men and 15 women). Most patients combined benzodiazepines with heroin or other opiates (64 patients, 58 male and 6 female), 23 patients combined BZD with cannabis (16 male and 7 female). 17 patients combined more than 3 classes of substances of abuse (14 men, 3 women), 10 patients combined BZD with alcohol (8 men and 2 women) and only 6 patients combined BZD with NPS (all being men).

Polyconsumption and other types of substances of abuse. The study included 41 patients (representing 1.59% of all patients in the study) who used other drug categories such as amphetamines, cocaine, LSD, ecstasy, inhalants, or ketamine. Their distribution by sex is shown in Figure 3.

Regarding policonsumption, a total of 752 patients were registered, of which 663 were men (representing 88.16% among polydrug consumers and 25.77% of the total patients included in the study) and 89 were women (representing 11.83% among polydrug consumers and 3.46% of all patients included in the study).

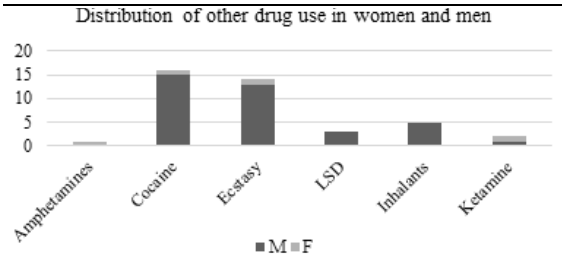

Figure 3.
Distribution of other drug use in women and men

Consumption trends. Following the analysis of the study group, the trend in consumption during the years 2015 - 2021 was observed by analysing the increase/ decrease of consumption. Among the study participants, there were 357 consumers between 2015 and 2016, an increase of 5.32% was registered in 2017 (compared to the end of 2016), 420 consumers were registered between 2017 and 2018 and 433 for 2019. Although, the study has overlapped with COVID-19 pandemic in 2020 no decrease in consumption was outlined. Unexpectedly, the use of drugs has reached its highest increase (+ 25.87%) over the past five years.

Indicator: hospitalization symptoms

Statistical correlation between hallucinations/bizarre substance addictive behaviour. The patients included in the study showed a multitude of clinical signs at admission, depending on the substance of abuse. Because the clinical symptoms are almost similar for all classes of drugs that were evaluated in this study, we focused on one particular symptom to investigate if there were statistical differences among groups. A chi-square test for independence was performed to assess the relation between hallucinations (auditory, visual, or both), bizarre behaviour and the type of substance of abuse. We analysed the occurrence of these changes among users of legal highs, cannabis, BZD and others (opiates and alcohol). We assimilated alcohol and opiates to the "other" category because they have a frequency of occurrence of less than 5. To assess if the variables are independent we considered the single consumption only, excluding the group who used multiple drugs. The null hypothesis stated that there are no differences between the categories of drugs, so the occurrence of the hallucinatory effect does not depend on the substance administered. The results were: χ^2 (3, 1820) = 312.9504. p-value < 0.00001 and the contributions to chi-square value were: legal highs 47 (12.14) (100.15), cannabis 35 (6.04) (138.92), BZD 8 (4.27) (3.26) and other drugs 21 (88.56) (51.54).

Indicator: withdrawal. Of the total number of patients included in the study, 564 patients (500 men and 64 women) had withdrawal symptoms at admission. A total of 393 such events were associated with opiate use, 107 with multiple drug use, 51 with alcohol use, 6 with legal highs use, 5 with BZD use, and only 2 were associated with cannabis use. A chi-square test of independence was applied to assess the relation between withdrawal symptoms and the drug used. The results are expressed as count, expected count, contribution to chi-square: 51 (24.72) [27.95] for alcohol, 5 (16.17) [7.72] for BZD, 6 (46.20) [34.98] for legal highs, 393 (301.21) [27.97] for opiates and 107 (173.70) [25.62] in the case of policonsumption. The Chi-square value is χ^2 (4, 2433) = 161.54. p-value < 0.00001.

Substitution treatment – dose in MMT, MPA (maximum period of abstinence)

Most of the patients included in the study are opiate users (a total of 1304 of both sexes) so many of them (402 patients, mean age: 31.67 ± 6.83 years (reaching a minimum of 18 years and a maximum of 50 years) have been previously included in MMT (methadone maintenance treatment). Regarding the dose of methadone in MMT, the mean daily dose is 72.78 ± 31.59 mg methadone/day (with a minimum of 10 mg methadone/day and a maximum of 160 mg methadone/day). Regarding the maximum withdrawal period, a total of 226 patients provided information, with a mean MPA of 33.68 ± 2.35 months (2.8 years ± 2.35 months).

Comorbidities

The correlation between comorbidities and the type of drug consumed was assessed by applying the CHI-square test. To assess the correlation of this effect with the single use of substances of abuse, the group of multiple drugs users was excluded from the test.

χ^2 (4, 1779) = 108.4794 and p-value < 0.00001 and therefore we reject the null hypothesis, that there is no correlation between variables. The variables are therefore dependent (comorbidities: HIV, HBV and HCV and use of certain categories of drugs): cannabis 5 (29.77) (20.61), legal highs 33 (59.85) (12.04), opiates 479 (392.15) (19.23), alcohol 8 (32.18) (918.17) and BZD 10 (21.05) (5.80).

Paraclinical examination

Patients included in the study were analysed for haematological and biochemical examination, urine summary examination and toxicological examination (rapid urine test).

Out of the total number of toxicological tests, 979 tests were positive for at least one substance (the test kit returns the qualitative result for amphetamine, marijuana, ecstasy, cocaine, opiates, methadone, or BZD).

Urine summary analysis was performed for the presence of bile pigments and/or urobilinogen in the urine. The categories of patients were compared depending on the drug consumed and the existence of a liver disease. The results were 11 (10.08) (0.08) for legal highs, 7 (6.35) (0.07) for cannabis, 32 (33.24) (0.05) for opiates, 6 (4.48) (0.51) for BZD and 34 (35.85) (0.10) for multiple drugs.

To assess the variation of the haematological and biochemical parameters, the Chi-square test of independence was applied. The study groups were users of legal highs, cannabis, opiates, BZD, alcohol, other and multiple drugs. The values obtained from the medical records of the patients were compared to the reference values for the interest parameters (Table II). The results are listed in Table III below.

For each parameter, the mean, standard deviation and homogeneity coefficient (CV) were calculated. Only LYM, MCH and MCHC have a homogeneity coefficient of less than 20%, namely LYM 13.22, MCH 13.01 and MCHC 4.55 respectively. For values of CV > 20%, then the group is not homogeneous, and the parameter cannot be used to characterize the entire group.

Table III

CHI-test – haematological and biochemical parameters in correlation with the substance of abuse

Parameter	χ^2 (DF, N) = Chi-square statistic value, p-value
Increase of ESR	χ^2 (6, 475) = 4.4216, p value = 0.351946
Increase of LYM	χ^2 (6, 500) = 0.3285, p value = 0.999347
Increase of GGT	**χ^2 (3, 452) = 12.5153, p value = 0.005816**
Increase of TGP	χ^2 (2, 452) = 0.3212, p value = 0.956001
Increase of TGO	χ^2 (2, 433) = 1.8149, p value = 0.403555
Increase of cholesterol	χ^2 (1, 239) = 3.2895, p value = 0.069726 **with Yates correlation:* χ^2 (1, 239) = 2.0828; p value .148965.
Decrease of cholesterol	χ^2 (2, 430) = 2.8163, p value = 0.244595
Increase of triglyceride	χ^2 (1, 430) = 0.5283, p value = 0.767871
Decrease of MCH	χ^2 (5, 504) = 0.8166, p value = 0.975962
Decrease of MCHC	χ^2 (5, 504) = 1.0161, p value = 0.961257
Decrease of urea	χ^2 (1, 371) = 0.0947, p value = 0.75833 ** with Yates correlation*: χ^2 (1, 371) = 0.0043; p value 0.947508

Cardiological examination

A total of 584 cardiological examinations were recorded, of which 319 (54.62%) showed at least one change in at least one parameter. To assess the correlation between the occurrence of cardiac events and the substance of abuse consumed, the Chi-square test for independence χ^2 was applied (appearance of cardiological changes *vs.* without cardiological changes). Chi-square value is χ^2 (4, 393) = 31.2219, p-value < 0.00001, so the variables are not independent: 36 (30.23) (1.10) for legal highs, 17 (13.60) (0.85) for cannabis, 111 (135.02) (3.95) for opiates and 111 (135.02) (3.95) for multiple drugs. The occurrence of cardiological changes was also analysed in correlation with the age of the patients. The mean age for patients with heart diseases is 30.54 ± 6.75 years with significant differences among groups: cannabis (24.82 ± 3.28 years), BZD (25.92 ± 4.59 years), legal highs (26.83 ± 6.31 years) and alcohol (40.71 ± 10.50 years).

Demographic characteristics – age and sex, age at the onset

There were no significant differences between males and females regarding the mean age but significant differences were outlined between mean age of the group (31.66 ± 5.65 years and ranges from 16 to 71 years) and mean age at the onset of use, the first one being significantly higher than the age at the onset of use (19.61 ± 6.14 years (min 8 years; max 48 years) which indicates long dependence/drug use period of time for the study group.

Type of substance of abuse

The study groups were unequal, both in terms of sex and in terms of the substance consumed, most of them being heroin users, which is explained by the specifics of the centre. Also, in terms of combining various groups of substances of abuse, the majority of the patients with poly-consumption were males.

Hospitalization symptoms

Statistical correlation between hallucinations/bizarre substance addictive behaviour. According to the Chi-square test, χ^2 (3, 1820) = 312.9504. p-value < 0.00001, therefore there are statistical differences between drug categories, cannabis users being more likely to develop hallucinations/bizarre behaviour, followed by legal highs users. The similarity between the two categories could be explained by the fact that the analysed categories of legal highs (synthetic cathinone and synthetic cannabinoids), as described above, mimic either the effects of cannabis or the effects of amphetamine. Also, patients described changes in perceptions and hallucinations experienced following the use of various substances, and most of these statements were associated with legal high consumption (17 out of 25).

Withdrawal. The Chi-square value is χ^2 (4, 2433) = 161.54. p-value < 0.00001 which means that there are significant differences among the study groups. According to the contribution to chi-square static, legal highs users are prone to develop withdrawal syndrome. Also, the results confirm that both opiates and alcohol consumption lead to psychiatric and physical dependence manifested as withdrawal syndrome. In the case of cannabis use, withdrawal syndrome is not present regularly, therefore only 2 patients had such manifestations.

Substitution treatment – dose in MMT (methadone maintenance treatment), MPA (maximum period of abstinence)

The mean daily dose of methadone in MMT is 72.78 ± 31.59 mg methadone/day. Although the mean methadone dose listed within the literature is approximately 90 - 100 mg/day, previous studies have also shown that moderate methadone doses are successfully used to stabilize the patients (50 - 60 mg/day) avoiding the appearance of abstinence syndrome on one hand, and, reducing possible interactions with other medicines, on the other hand, supporting, therefore, the results from this present work [30-34].

Comorbidities

Assessing the dependence of comorbidities on various groups of drugs, the result obtained is χ^2 (4, 1779) = 108.4794 and p-value < 0.00001, meaning that co-morbidities such as HIV, HBV and HCV are related to the use of certain categories of drugs. Although the highest contribution to Chi-square is associated with alcohol use, opiates consumption has the highest frequency in the study group. Route of administration is the major risk when transmissible diseases are taken into account, i.v. administration facilitating the transmission of contagious diseases among users. Regarding the high incidence of these comorbidities among users of multiple drugs (195 observations from a total of 730 investigations), this can be explained by the fact that this pattern of use targets in most cases, at least one drug predominantly with i.v. administration.

Paraclinical examination

Urine summary analysis. The urine was analysed for the presence of bile pigments and/or urobilinogen. No statistically significant difference among the groups was outlined, χ^2 (4, 241) = 1.2871. p-value 0.86356. Either the presence of bile pigments and/or urobilinogen in the urine may be related to the existence of liver disease (such as hepatitis and jaundice [35, 36]).

Haematological and biochemical parameters. Being a retrospective study with illicit drugs, a comparison before and after intake of these parameters was not possible. However, the data were compared with the reference values for healthy individuals (as described in "3. *Results"* section).

The relationship between these variables proved to be insignificant for most parameters, except for GGT (χ^2 (3, 452) = 12.5153, p-value = 0.0005816, legal highs 11 (12.69) (0.22); cannabis 2 (NA); opiates 36 (40.14) (0.43); BZD 1 (NA); alcohol 10 (3.95) (9.26); other 1 (NA); multiple drugs 37 (37.23) (0.00)). Alcohol is the substance that caused the highest frequency of increases in GGT values. This could be explained by the existence of liver diseases. Increased values for GGT can be also indirectly correlated with drug use, due to the route of administration (by injection) which significantly increases the risk of contracting a contagious disease (HIV, HBV, HCV). Similar studies support the outcome of our study where the increase of GGT in heroin addicts patients during methadone substitution treatment has been outlined [26]. Additionally, GGT is a well-known biomarker for heavy alcohol intake [27]. According to our study GGT proved to be the highest chi-static value for alcohol intake, a result sustained by the outcomes of previous experimental studies that have shown a causal relationship between increased GGT values and heavy alcohol intake [29]. Moreover, we concluded that values GGT values are mostly influenced by contagious disease, regardless of the drinking status, as placebo-controlled trials have also shown [28].

Only LYM, MCH and MCHC have a homogeneity coefficient of less than 20% and can characterize the study group. It is necessary to analyse these parameters' evolution before and after intake to assess the dependence on the type of drug or if the changes are related to pre-existing comorbidities. This kind of monitoring is possible for methadone only (which is used in substitution treatment for heroin addicts) as other substances are not suitable for such analysis due to their illicit and addictive character. Although no significant differences were outlined among groups, there was highlighted the homogeneity of decreased MCH and MCHC values among all patients included in the study. Regarding the changes that appear on haematological and biochemical parameters after drugs of abuse intake, more work is needed in the field as only a few research papers have shown the effects of various groups of drugs on the hematopoietic system. Chronic alcohol consumption leads to a reduction of haemoglobin levels and only MCV and MCHC appeared to be impacted (increased values compared to controls) [37]. In conclusion, some red blood cells indices deteriorate, and anaemia appears in alcoholics, but also after various drug of abuse intake. Regarding the exposure to heroin, there were no statistical differences among erythrocyte indices in previous studies [38]. Regarding the increased LYM values, that could be explained by the fact that most of the patients have a contagious disease, such as HIV, HVB, or HVC.

Cardiological examinations

The results of the study have shown that the variables are not independent, as χ^2 (4, 393) = 31.2219, p-value < 0.00001. We conclude that the group of alcohol users is more prone to cardiac events than other groups. Also, in the case of alcohol users, the fact that the mean age for patients with cardiac events is significantly higher than the mean age of the entire study group, outlines that these cardiac manifestations can be attributed both to age and to the toxic action of alcohol.

ECG abnormalities are frequent in drug abuse use. Although we do not have information on the cardio-

vascular history of the patients prior to drug exposure, similar to other studies [17], the most frequent ECG abnormalities in our study opiate addicts group are branch block (12.18%), axes deviation (10.31%) and infarction (10%), 34.68% having an abnormal ECG. Almost 11.11% of the patients included in our study who used cannabis have had an infarction while 48.14% have presented abnormal ECG, reinforcing the novel findings in the field that underscore the harmful effects of cannabis [38]. The most common ECG abnormality for NPS users is branch block (18.33%), but axes deviation, an increase of QT interval and P-wave and ST-elevation were also identified among the group. For legal highs, although there is a lack of studies regarding electrocardiographic abnormalities in cathinone use, various case reports [40, 41] highlighted manifestations such as tachycardia, bradycardia, hypertension, myocardial infarction, arrhythmias and cardiac arrest after synthetic cannabinoids use. Results similar to ours were also outlined in different case reports while investigating the electrocardiographic parameters in patients consuming synthetic cannabinoids: P-wave higher dispersion [42, 43], increased QT interval [43, 44] and fibrillation [45, 46].

Conclusions

Conclusions can be drawn correlating different categories of substances of abuse and symptomatology with changes in different paraclinical, haematological, biochemical and urinary parameters. Highlighting the parameters that are statistically influenced by the category of drug of abuse consumed could characterize the different types of consumers but could also serve as a support for future research.

Although it is a retrospective study, its importance is significant because an analysis of patients before and after drug intake is impossible (due to the addictive and illegal nature of the substances analysed) and it would not be an ethical approach.

The study opens new perspectives for future studies on correlating the variable parameters (haematological and biochemical, urinary, psychiatric, psychological and cardiological) with the chemical structures of the consumed compounds detected by high-performance analysis methods. One new direction of research could be the quantification of plasma and/or urine levels of various synthetic cannabinoids and cathinone and of their metabolites for patients in emergency rooms correlated with the variation of the above-mentioned parameters. Another perspective could be a follow-up study measuring the variable parameters (haematological and biochemical, urinary, psychiatric, psychological and cardiological) before and during substitution treatment with methadone.

Limitations

By extrapolating the results of this study to the use of different classes of drugs among the general population of drug users, several limitations can be highlighted. First of all, the groups are unequal, both in terms of sex and the substance consumed, most of them being heroin users, which is explained by the specifics of C.E.T.T.T. "St. Stelian" detoxification centre, Bucharest, Romania. Secondly, many of the toxicological tests performed on urine samples had negative results and the substance could not be detected (due to either the long time between intake and urine collection or because the current methods of analysis do not allow the detection of certain classes of substances such as legal highs). Thirdly, being a retrospective study, the analysis of biochemical, haematological and urinary parameters was performed compared with the standard reference values. For a better analysis, medical data from patients before drug intake would provide a more accurate assessment of the direct influence of these substances of abuse on the various parameters. Finally, the data collected are not correlated with chemical structures for incriminated substances as these were not available at the time of hospitalization, but this can represent a new objective for future research in the field.

Conflict of interest

The authors declare no conflict of interest.

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