MEDICAL UNIVERSITY - VARNA " Prof. Dr. PARASKEV STOYANOV"

FACULTY OF PHARMACY

Department of Pharmacology, Toxicology and Pharmacotherapy

Stanislava Angelova Georgieva, MPharm

CHARACTERISTICS OF ACUTE MEDICINAL POISONING CASES IN VARNA DISTRICT OVER A 30-YEAR PERIOD

ABSTRACT

of a dissertation for the award of educational and scientific degree "Doctor" in the specialty "Toxicology"

Supervisors:

Prof. Dr. Petko Penkov Marinov, MD

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Varna 2021

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The dissertation has been presented at a meeting of the Department of Pharmacology, Toxicology and Pharmacotherapy at the Medical University - Varna and was addressed to the Scientific Jury.

The dissertation includes 160 pages, 25 figures and 20 tables. The bibliography covers 260 titles.

The public defense of the dissertation will take place on …… by ……..at an open meeting of the Scientific Jury.

Contents

List of Abbreviations

4-AA - 4-aminoantipyrine

4-FAA - 4-formylaminoantipyrine

4-MAA - 4-methylaminoantipyrine

AAPCC NPDS - The National Poison Data System of the American Association of Control Centers

AC - Activated charcoal

ADI- acute drug intoxication

ADP- acute drug poisoning

AEDs-oral antiepileptic drugs

ALAT - alanine aminotransferase

ASAT - aspartate aminotransferase

BDZ – Benzodiazepines

CCB - Calcium channel blockers

CDI - Combined drug intoxications

CNS - Central nervous system

CVD - cardiovascular diseases

DSFab - Digoxin - specific antibodies

ECG – Electrocardiography

ECMO - Extracorporeal membrane oxygenation

ECTR- Extracorporeal treatment techniques

EHIS - The European System for Health Interviews

GABA - Gamma aminobutyric acid

GIT- gastrointestinal tract

HIET - High-dose Insulin Euglycaemic Therapy

ICD - International Classification of Diseases

IVLT- Intravenous Lipid Emulsion Therapy

NAPQI is N-acetyl-p-benzoquinoneimine

NLP - Natural Language Processing - Natural language processing

NMS - Neuroleptic malignant syndrome

NSAIDs - non-steroidal anti-inflammatory drugs

PSS- Poison Severity Score

SE - Status epilepticus

SNRIs - serotonin and norepinephrine reuptake inhibitors

SSRI - Selective serotonin reuptake inhibitors

SVM - Support Vector Machines - Machines with support vectors

TCA- tricyclic antidepressants

WHO - World Health Organization

Introduction

Poisoning is a significant public health problem. According to WHO data, in 2016 more than 1,206,000 people died as a result of accidental poisoning. Of these deaths, 84% occured in low- and middle-income countries. The causes of poisoning are many: human error, industrial, intentional and accidental. The most common toxic agents worldwide are pesticides, drugs (sedatives, painkillers, antidepressants, etc.), chemicals (acids and copper sulfate), alcohol, plant toxins, and household chemicals. There are significant differences in patterns of poisoning between different countries. In developed countries, the annual prevalence of accidental or deliberate poisoning cases in humans varies between 0.2 - 9.3 exposures to poisoning per 1 000 people and continues to increase annually worldwide as case reporting and registration increases.

Acute poisoning is a condition of damage whose toxic effects occur almost immediately, within hours of exposure. It is a common cause worldwide for seeking emergency medical care and hospitalization, and its morbidity and mortality is becoming a major public health problem in many countries. The World Health Organization (WHO) estimates the total number of acute accidental poisonings worldwide at 2-3 million cases per year, of which 1 million severe poisonings, leading to 20,000 deaths per year. The estimated number of intentional poisonings is about 2 million, of which approximately 200,000 are suicides.

The high frequency of accidental or intentional poisonings with drugs from different groups are a prerequisite for the development of specific programs for diagnosis, treatment and prevention of poisoning in different countries. The main elements of these programs are the identification of toxic hazards that exist at the local level (in order to establish preventive measures), the diagnosis of poisoning and the treatment of patients. Special attention should be paid to the relative share of poisonings to the total number of suicides. The incidence of intentional ingestion of suicide drugs is particularly high in the Nordic countries and the United Kingdom, and is relatively lower in Eastern Europe and Central and South America.

The total population of Bulgaria amounts to 6,916,548 people, according to the National Statistical Institute as of 31.12.2020. The northeastern region is inhabited by 922,230 people, and Military Medical Academy - Varna is the only healthcare institution in northeastern Bulgaria with a specialized clinic for treatment of acute poisoning and toxic allergies.

In Bulgaria, the medical and social aspects of acute poisoning are related to the real problems of society. Mortality due to exogenous poisonings is indicated as 1 per 100,000 of the population according to the National Statistical Institute for 2019. The importance of this fact increases due to the unfavorable demographic situation in Bulgaria (-9.5 ‰ natural increase in 2020). The toxicological situation for the last few years is characterized by dynamics depending on the frequency, structure and clinical manifestations of exogenous poisonings, as well as the socio-demographic characteristics of the victims.

However, due to the imperfection of the reporting of acute poisonings, to date there is no objective picture of the situation, both at central and regional level.

Epidemiology of acute drug poisoning

Data from the World Health Organization (WHO) show that the total number of acute accidental poisonings worldwide varies from 2 to 3 million cases per year, of which 1 million are severe poisonings, leading to 20,000 deaths per year, while the estimated annual number of intentional poisonings is about 2 million as a result of 200,000 suicides. It should be noted that patients with acute poisoning represent 15-20% of the total number of patients who are hospitalized annually. The exact number of cases may be higher, as most cases of poisoning actually go unreported. In Western Europe, twice as many patients are hospitalized for acute poisoning than for myocardial infarction, and the mortality rate for this pathology is higher than for infectious diseases and traffic accidents. Current statistics show an increase in the incidence of acute poisoning over the last decade, in contrast to the share of natural, man-made and socio-political emergencies.

Currently, in developed countries the most common acute exogenous intoxications are drugs (60%), which can be explained by the fact of their easy availability and their presence in every home. Both prescription and over-the-counter drugs are used worldwide for self-poisoning, mainly in urban areas. The most commonly used medicines are drugs which act on the central nervous system, such as antipsychotics, antidepressants, barbiturates and benzodiazepines; followed by analgesics mainly paracetamol, antiepileptic drugs such as carbamazepine, antiseptics and disinfectants, antimalarial drugs such as chloroquine and others.

Morbidity and mortality in each acute case of poisoning depends on a number of factors such as the nature of the poison, the dose consumed, the availability of medical facilities, treatment by qualified personnel and the time interval between poisoning and the provision of medical care.

Purpose, tasks, hypotheses

Purpose

The aim of this dissertation is to study, analyze and derive the main characteristics and epidemiology of acute drug poisoning cases in Varna region, registered in Clinic for intensive treatment of acute poisoning and toxicoallergies at the Military Medical Academy in Varna for the period 1991-2020 to improve measures for their prevention.

Research tasks

To achieve the set goal, the following tasks were performed:

1.1 To study, analyze and report the frequency and structure of acute medicinal intoxication cases in the Varna region for a period of 30 years;

1.2 To study and determine the leading groups of drugs and their percentage distribution in the total volume of the study;

1.3 To monitor and analyze the dynamics and lethality of ADIs

1.4 To study and derive the demographic characteristics of patients with ADIs

1.5 Analysis of the pathology and models for diagnostic-therapeutic behavior in the characteristic drug intoxications;

1.6 To monitor and analyze the trends and costs of poisoning in order to assess the appropriateness and quality of care,

1.8 To structure an approach for automated analysis to extract content from natural language medical history and blood tests, in order to prevent poisoning in the combined use of medicinal products.

Object of the study

The object of the study are 6977 patients with ADIs, admitted for treatment in the Clinic for intensive treatment of acute poisoning and toxicoallergies at the Military Medical Academy in Varna for the period 1991 - 2020.

Inclusion criteria

- Age > 13 years;

- Main complaint of acute poisoning;

These criteria aim to better focus the study and do not reduce the merits of the study and the value of its results, as patients under 13 years of age are admitted and treated in pediatric clinics.

Research methods and tools

This part provides a description of the activities and the experimental setup for presenting the characteristics of acute drug poisoning in the Varna region for a 30-year period, for achieving the research goals and for solving the formulated tasks:

- Summarizing AMIs data using descriptive and inferential statistics;

- Approach to reporting data uncertainty, which may be characterized by error propagation if the variability of the collected data is propagated in subsequent calculations;

- Using probability distributions to describe data variability;

- Approach to using a statistical sample of AMIs cases among the Varna population to generate statistics and conclusions about the population of the Varna region, using assessment procedures and hypothesis tests;

- Approach to using regression analysis to describe a linear correlation between variables in the statistical sample;

- Approach to the use of computers and modern software platforms in statistical calculations.

The documentary method is used for analysis of literature sources, documents and regulations.

Statistical methods were used to reveal the nature, dependencies and trends of the observed phenomena and to interpret the results obtained, which are a model of poisoning, on the basis of which in the future to create an expert system for the potential risk posed by AMI:

• descriptive analysis - a descriptive analysis of all variables was performed, the quantitative variables being expressed as mean, frequency and percentage. Characteristics such as gender, age of patients, intentional or accidental overdose were analyzed and considered statistically significant for all comparisons.

Microsoft Excel, LibreOffice Calc, Google Sheets and SPSS (version 17.0) were used for computer-aided evaluation of statistics.

Descriptive statistics provide methods for presenting and summarizing the measured data by calculating specific sample characteristics determined solely by the type of data. The data collected in the experiment are either qualitative (from a certain category) or quantitative (numerical). Raw data are presented in the form of figures and tables and can be summarized by presenting the average value covering the development trend for the variability, together with the number of observations.

The inference statistics are summarized for the general population and are based on the training sample. For this purpose, two main methods are used: evaluation and testing of hypotheses. Evaluation procedures are used to calculate an unknown parameter of the general data set, such as the expected value of the baseline distribution, using the average value calculated from the samples collected from the sample (point estimation). Then, a confidence interval is built around this unit value, covering the value of the general population parameter with a predefined confidence level. Hypothesis testing (significance test) - for this purpose, the probability of explaining the difference observed between the two groups is explained only by chance. A distinctive feature of statistical decision-making is that uncertainty cannot be eliminated, as decisions have to be made on the basis of limited samples.

Approach for automated analysis for content extraction from natural language medical documents available to the patient

In recent years, Artificial Intelligence (AI) and Machine Learning (ML) technologies have seen unprecedented growth due to a number of factors. Image recognition, data classification and natural language processing (NLP) technologies are widely used to aid in human speech recognition; creation of robots for automated answering of questions and mood analysis are several of the areas of application. NLP is also one of the tools that serves to enrich the analysis in journalism to unlock additional functionality in the behavior of the system. For example,

applications are known that support the word processing of log files to identify common clusters or data patterns.

This chapter describes a proposal for an NLP approach to create a mathematical model for assessing the risk of drug intoxication depending on the patient's medicinal products, dietary supplements in combination with or without ethanol. With the great advancement of Pandas data processing libraries in the Python programming language and the rapid development of NLP libraries for natural language information processing, it has become possible to develop a computer application for the benefit of the patient, doctor and pharmacist. Pandas is an open source library that provides easy-to-use data structures and data analysis tools in the Python programming environment. There are a number of good open source libraries for NLP in Python. The scikit-learn library was chosen because it has a broad set of machine learning tools for efficient data retrieval and word processing.

The practical application of the proposed approach is the possibility of creating a database of combined drug intoxications, which can be supplemented and changed.

Data input

The data that are entered are text from part of the epicrisis, prescription and data from an outpatient list. Roles: Patient - mobile application, electronic file sharing; Doctor: integration with the coordination center system; Pharmacist: integration with a coordination center system. With this process the described structural diagram in fig. 2.

Pre-processing of the data may include checking for spelling errors and searching for n-grams, which can bring normalization of the data at the input.

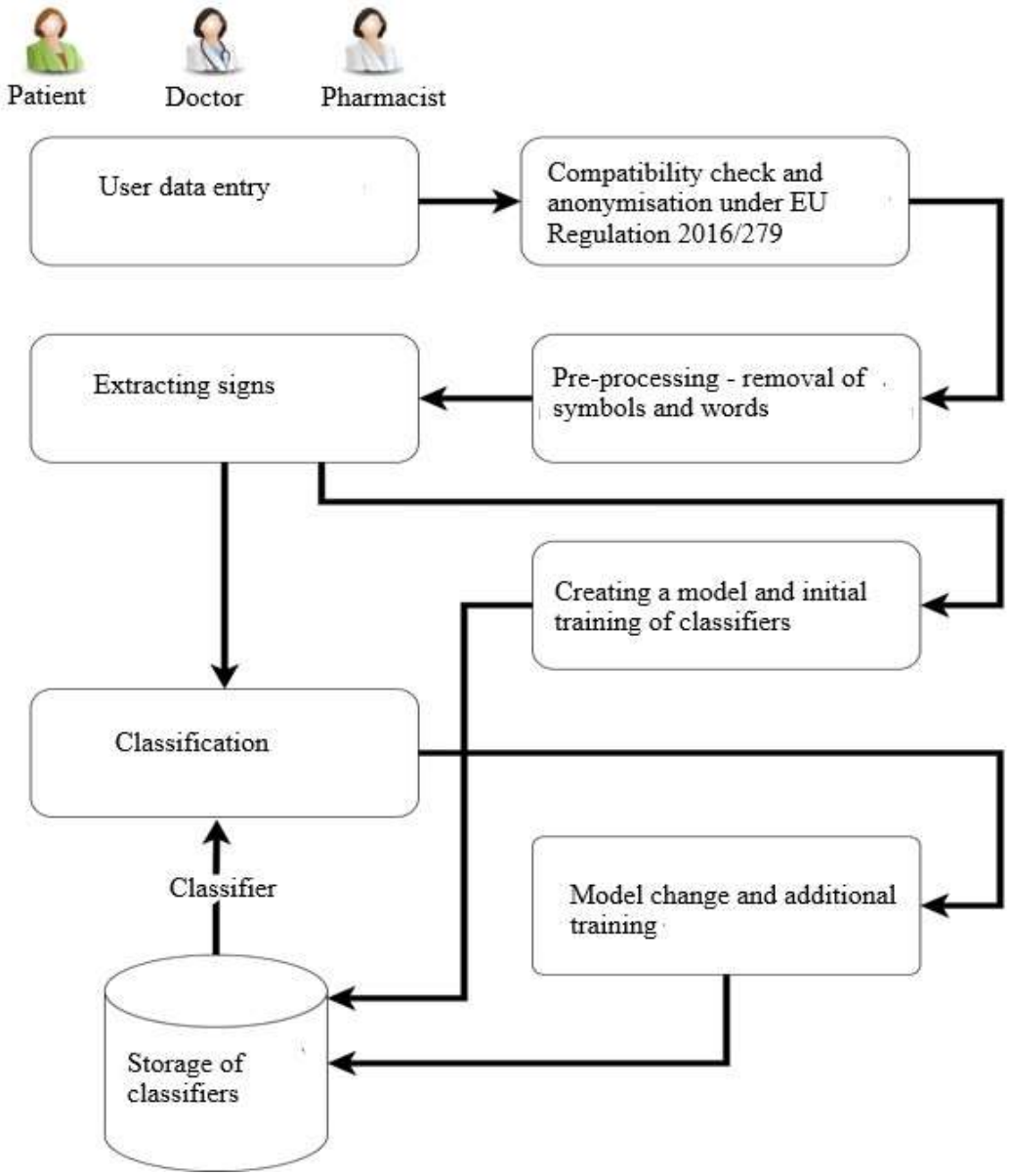

FIG. 1 Diagram of a proposed system for training classifiers of text from patient documents for the purposes of automated risk assessment in a poison control coordination center

Application structure for automated poisoning risk assessment

Once the classifiers are trained on a sufficient number of patient data, it is possible to create an automated mobile application. It is proposed that the data can be scanned with a mobile phone, processed in advance, sent via an encrypted connection to the cloud infrastructure of a coordination center, classified and transmitted for feedback to a pharmacist, doctor and patient. An opportunity can be created for further training of the system with the help of new data provided by a doctor, pharmacist or patient.

Training time and inclusion criteria

The study was conducted in the city of Varna by the author, using for analysis the medical histories, personal ambulatory cards of poisoned patients admitted for treatment, with the permission of the Chairman of the Ethics Commission at the Military Medical Academy in Varna.

Results

Between 1991-2020, 6977 patients with acute drug intoxications (ADI) were admitted to the Clinic for Intensive Treatment of Acute Poisoning and Toxic Allergies of the Military Medical Academy in Varna. During the analyzed period of the preliminary study, the average frequency of cases per year was 232.

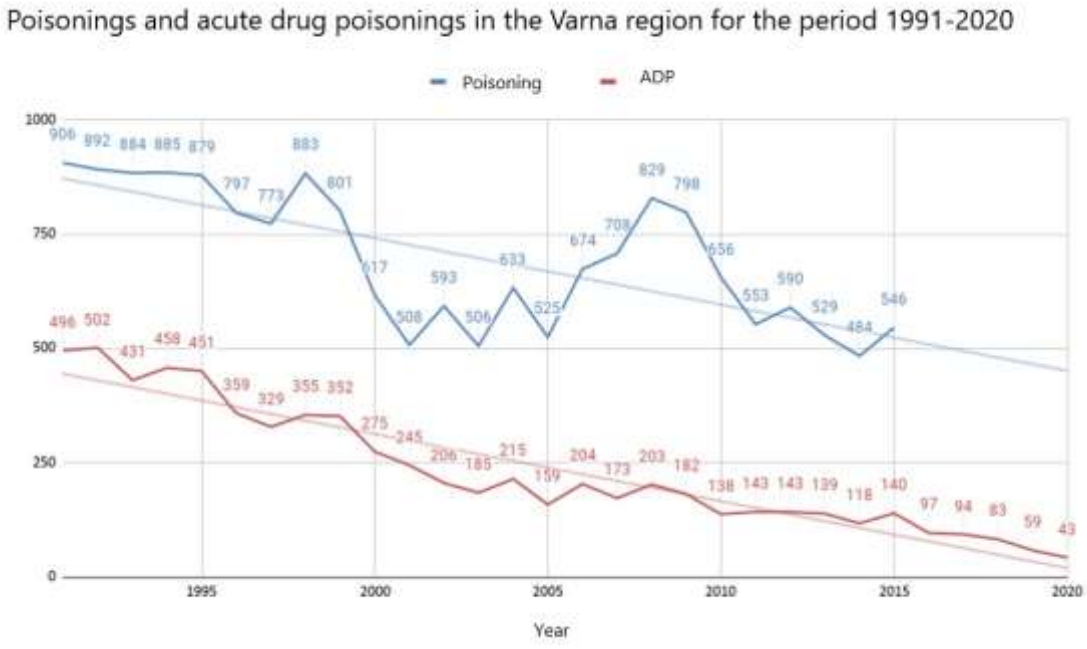

Fig.2 Graphical representation of ADI in relation to the total number of poisonings in Varna region for a 30-year period

The close to linear trend of decreasing cases of poisoning is due to various factors:

- The social, economic and cultural characteristics of the population of Varna region

 demographic factors

 negative natural growth (- 5.7% for 2020), according to NSI data

 population aging (NSI) and permanent emigration of the young and able-bodied population

 Prevention

 especially in recent years there has been improved prevention of storage of drugs and food supplements at home.

Prevention can be achieved by raising awareness and information about the risks of overdose of one or more medicinal products with / without alcohol sharing. Educational and counseling campaigns could provide healthcare professionals (doctors, pharmacists, nurses, etc.) with the necessary knowledge on risk assessment of overdose and early identification of high-risk patients.

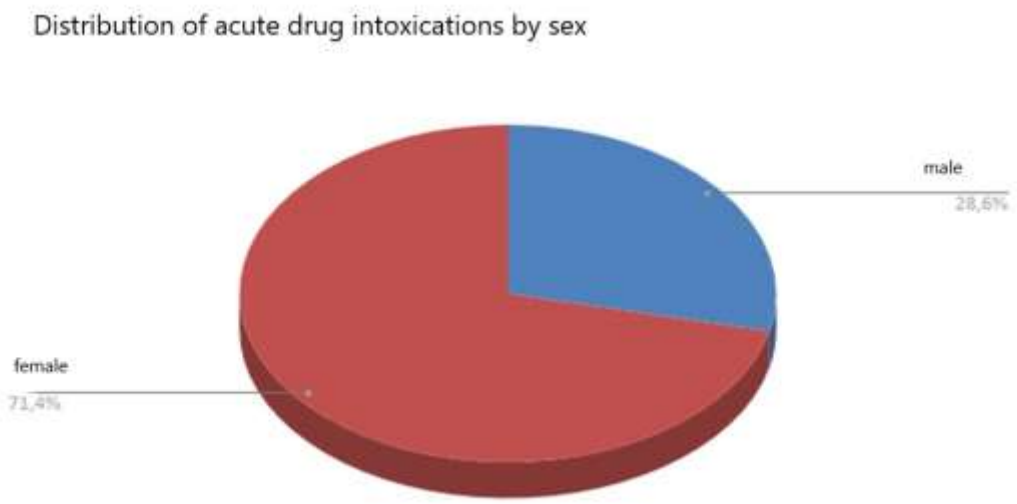

FIG. 3 Distribution by sex of the cases of ADI in the Varna region for a 30-year period (1991-2020)

The following results were reported in terms of gender distribution - 71.4% of intoxications were observed in women, compared to 28.6% in men. Women are most affected by poisoning as shown by the graphs. The figure shows a stable and significant predominance of women in both intentional and accidental (involuntary) overdose. This trend is determined by the general socio-demographic factors such as age, income level, employment status, education, marital status and indicators at the state level - social security, household expenditures.

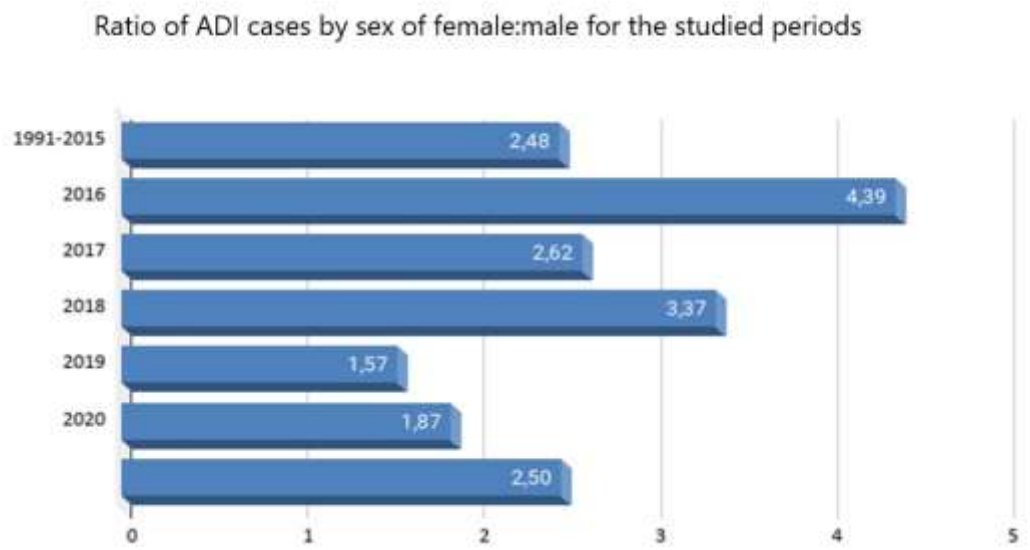

FIG. 4 Ratio of cases of AMI by sex female:male for the studied periods

Women are more often diagnosed and hospitalized as a result of poisoning, as shown by the graphs, as the average ratio for the 30-year period, women: men is 2.50: 1 (Fig. 4). There is a steady and significant predominance of women both in those treated for intentional poisoning and in those who have inadvertently accidentally overdosed on drugs. The analysis shows that young women are twice as likely to be victims of suicide drug poisoning than men, especially during adolescence. The reasons for this can be various: more frequent depressions, vulnerability, method of attracting attention, conflicts with a partner, disputes in training or at work, etc. With the decrease of the cases in the last 2 years of the observed period, the ratio decreases accordingly.

The clinical manifestations of acute drug toxicity have been found to be more or less the same in men and women, and their management follows the principles of good practice in clinical toxicology.

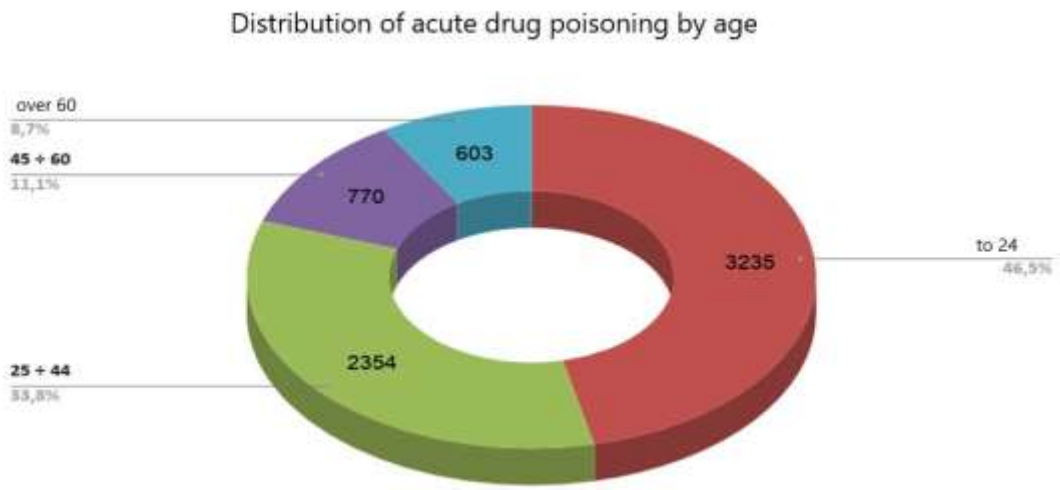

Fig.5 Distribution of ADIs cases by age for the years 1991 – 2020

The largest number of admitted patients with acute poisoning falls on the age groups: up to 24 years of age (46.37%) and 25-44 years (33.73%). These age groups maintained the leading position throughout the study period (Fig. 5). It can be noted that these are patients of active working age, and the widespread tendency of the population to self-medicate, combined with ignorance, is the basis for the tendency to drug intoxication, causing mental and physical disabilities.

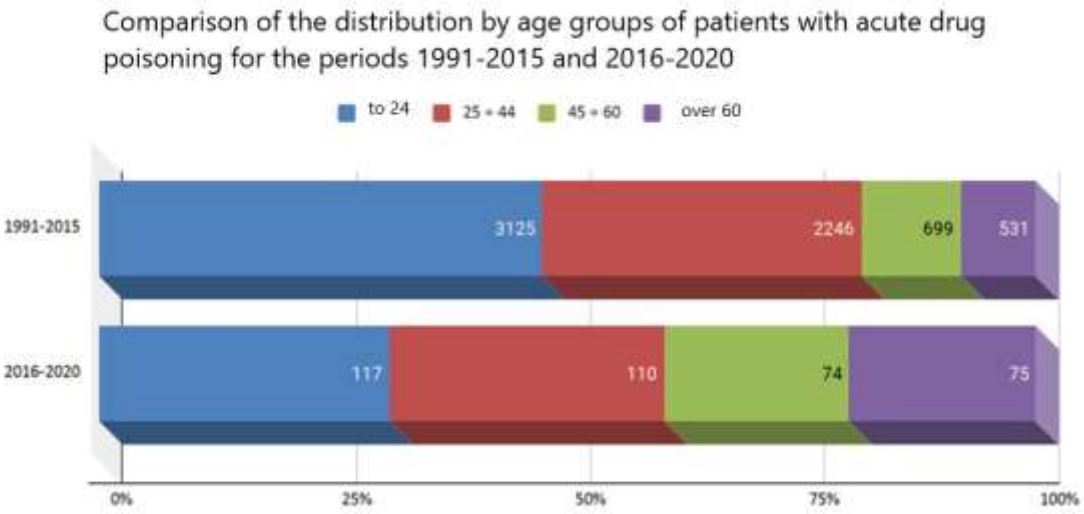

FIG. 6 Comparison of the distribution by age groups of patients with ADP for the periods 1991-2015 and 2016-2020.

There can be a positive dynamics of reduction in the number of patients in this age group in the last 5 years - 30% in the age group up to 24 and 25-44, compared with 47.3% (up to 24 years) and 34%) for the period 1991-2015 (Fig. 6) and (Fig. 7)

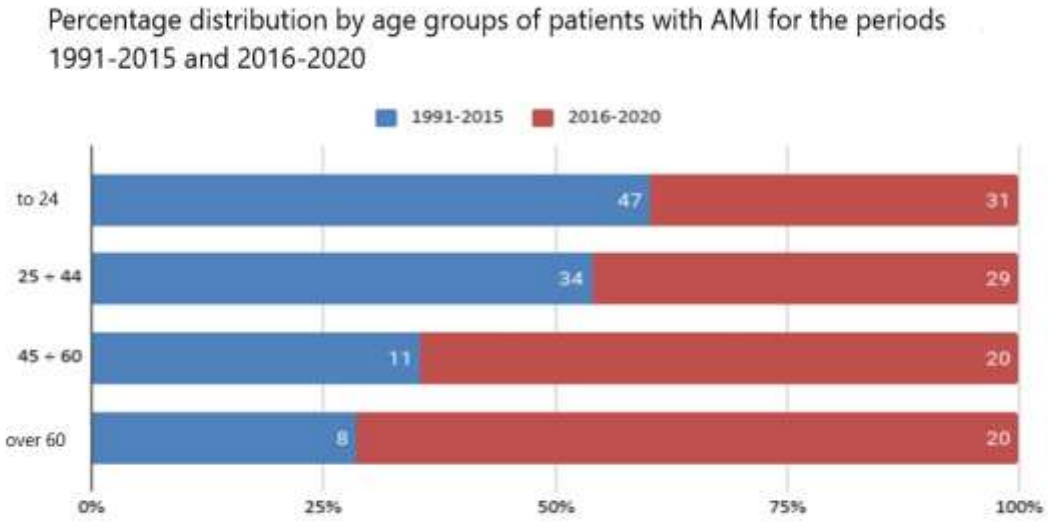

FIG. 7 Percentage distribution by age groups of patients with AMI for the periods 1991-2015 and 2016-2020.

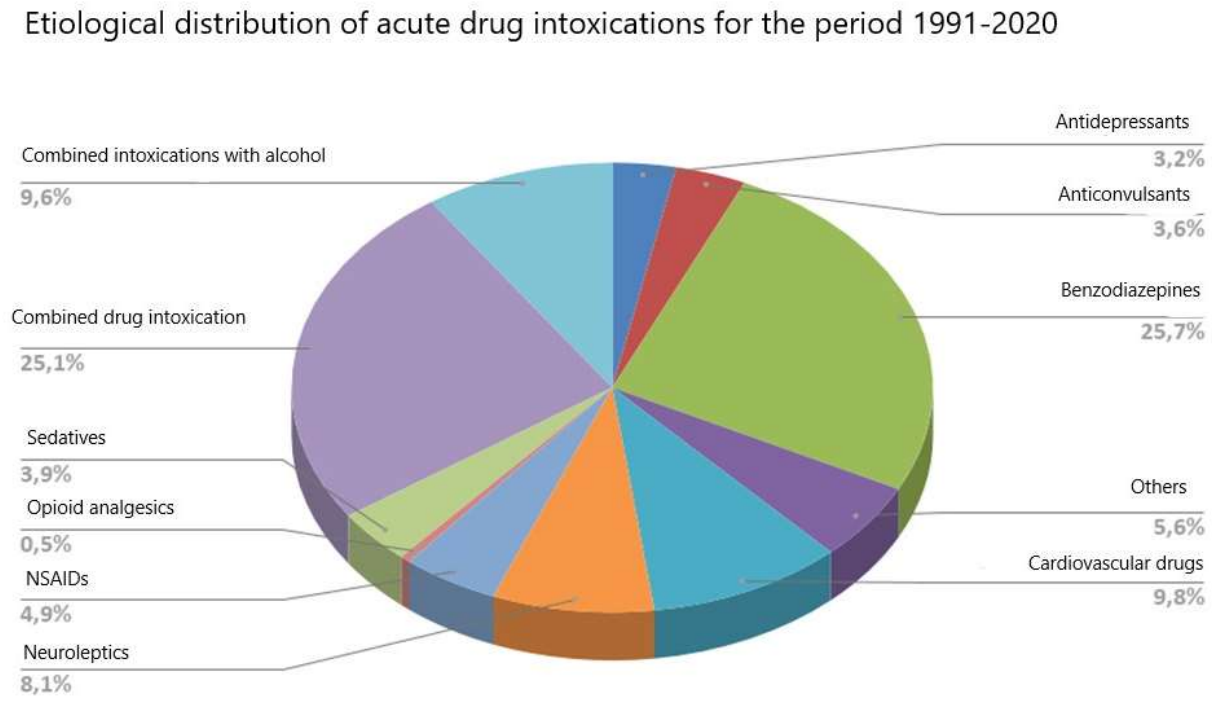

Fig.8 Etiological distribution of ADI cases from 1991 to 2020

Acute drug intoxications are divided by etiology into 11 groups - benzodiazepines, hypnotics, neuroleptics, antidepressants, anticonvulsants, nonsteroidal anti-inflammatory drugs / NSAIDs /, opiates, cardiovascular, mixed drug intoxications / drug intoxication and intoxication. antibiotics, vitamins, hormones, etc./ For the period 1991-2020 the most numerous are benzodiazepine

poisonings (25.7%), followed by mixed drug intoxications (Fig. 8). The results of the treatment of the patients were favorable for 99.29% of the cases, while 0.71% of the patients died (50 cases).

Benzodiazepines (BZD)

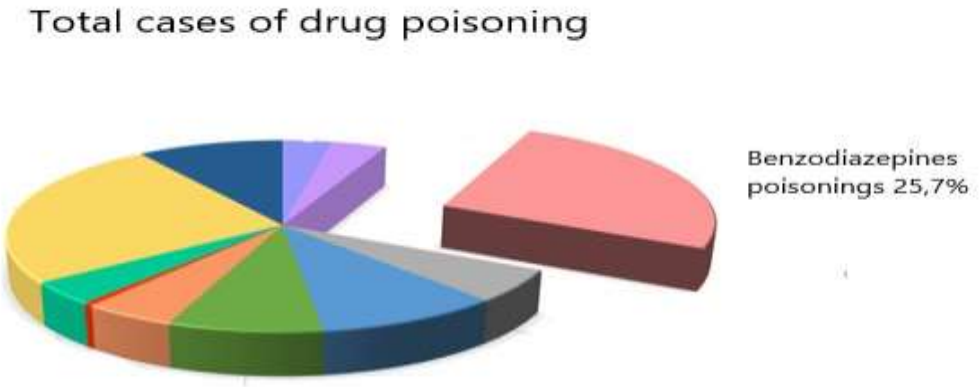

Fig. 9 Percentage of BDZ poisonings in relation to all ADIs

Since their introduction in 1960, benzodiazepines (BDZ) have been widely used with various indications - anticonvulsant, anxiolytic, antidepressant, alcohol and nicotine withdrawal, insomnia, muscle relaxant, neurosis, emotional stress, phobias and others. They are often used in combination with other drugs such as pre-anaesthetic agents. Their diverse application and widespread use make them one of the most common causes of acute poisoning. For this reason, they represent the largest percentage of all drug poisonings - 25.70%.

Table 1. Medicinal products containing benzodiazepines on the Bulgarian market

Diazepam	Diazepam tablets 5/10 mg X 10 pcs Diazepam Sopharma 5 mg / ml solution for injection 2 ml x 10
Midazolam	Midazolam 1 mg / ml solution for injection Midazolam 5 mg / ml solution for injection - 3 ml x 10 Midazolam 5 mg / ml solution for injection / infusion
Bromazepam	Lexotan 3 mg tablets x 30
Alprazolam	Xanax 0.25 / 0.50 mg tablets x 30

Lorazepam	Lorapam 1/ 2,5 mg tablets x 10
Clonazepam	Clonazepam 0,5/ 2 мг tablets x 30 Clonazepam 1 mg / ml solution for injection / infusion 1 ml x 10

Concerns about the lethal outcome and the health consequences of long-term use of benzodiazepines for (eg more than two to three weeks), their combination with opioids and / or alcohol, etc. are worrying. Although subject to a special prescribing and dispensing regimen (green prescription form), benzodiazepines are among the most common causes of acute intoxication.

Symptoms of isolated benzodiazepine overdose may include central nervous system (CNS) depression, slurred speech, ataxia and altered mental status, dizziness, and rare respiratory depression. Combination with ethanol leads to significant respiratory depression and airway compromise.

Diagnostic tests for acute poisoning include: complete blood count, urine test, ECG, chest X-ray, in the presence of respiratory depression.

The management of acute benzodiazepine poisoning follows the general principles of maintenance treatment and monitoring, airway maintenance, gastric lavage with activated charcoal and others.

There is a specific antidote for benzodiazepine poisoning - Flumazenil. Flumazenil is a competitive BDZ receptor antagonist and accelerates recovery from benzodiazepine sedation and respiratory depression up to 1-2 minutes after intravenous administration. Adverse reactions to Flumazenil may include agitation, gastrointestinal symptoms, supraventricular arrhythmia and convulsions. Flumazenil can cause acute withdrawal syndromes in those with chronic benzodiazepine dependence, which can be life-threatening.

Complications of benzodiazepine toxicity include: respiratory arrest, aspiration pneumonitis, rhabdomyolysis, death.

Combinations of drugs

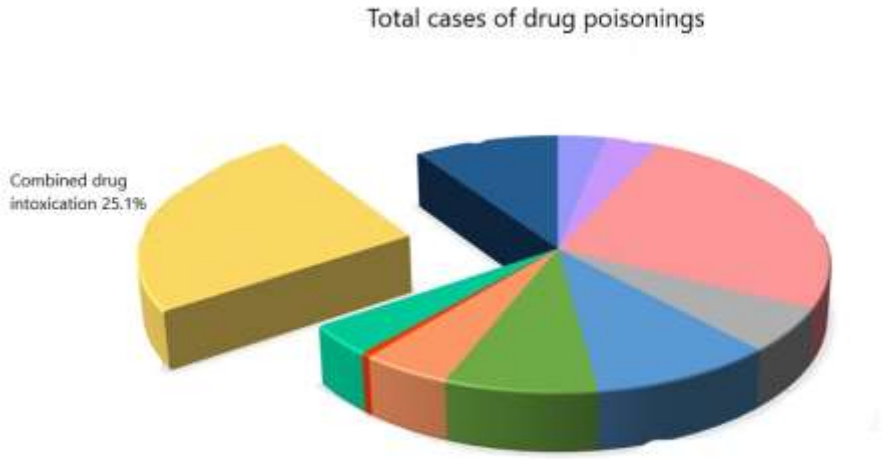

FIG. 10 Percentage of combined drug intoxications compared to all ADIs

Current EU population data show that the proportion of older people (aged 65 or over) is 20.3% (an increase of 2.9 percentage points compared to 10 years earlier) by 2019. The largest Shares of persons aged 65 and over in the total population were reported in Italy (22.8%), Greece (22.0%), Portugal and Finland (21.8% each). The process of population aging continues in Bulgaria. At the end of 2019, the persons aged 65 and over were 1,504,088, or 21.6% of the country's population. Compared to 2018, the share of the population in this age group increased by 0.3 percentage points. The aging process is more pronounced among women than among men. The relative share of women over the age of 65 is 25.1%, and of men - 17.9%.

Combined drug intoxication (CLI) occurs when two or more substances are taken at the same time and can lead to serious life-threatening conditions, including death. In the study, they are second in prevalence among all drug poisonings (25.1%). As for the last 5 years of the period the number of combined medicinal products, OTC - products and food supplements varies between 2 and 9 pieces, which is a prerequisite for complicated diagnosis and treatment.

An overdose can occur when too much medicine is accidentally or intentionally taken, the wrong medicine is swallowed, more than prescribed is taken, or the wrong combination of medicines is given incorrectly. Analgesics, antihypertensives, multivitamins are common drugs used in combined drug poisoning.

Potentially dangerous and deadly drug combinations are:

- The interaction between two serotonergic drugs that act by different mechanisms, such as an SSRI or a serotonin / norepinephrine reuptake inhibitor (SNRI), together with tramadol, trazodone,

dextromethorphan or linezolid, causes the so-called serotonin syndrome. Characteristics of serotonin syndrome include changes in mental status, neuromuscular hyperactivity, and autonomic hyperactivity.

- Interaction between statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) and CYP3A4 inhibitors (fibrates - especially gemfibrozil, azole antifungals, amiodarone, macrolides - erythromycin and clarithromycin, paryrichycin and proteaznito, proteases. - verapamil and diltiazem). There is a significant increase in the risk of rhabdomyolysis, which is characterized as a severe and even life-threatening pathological condition, in which there is myolysis of the striated muscle tissue and the release of large amounts of muscle protein myoglobin in the blood. Simvastatin and lovastatin interact most frequently with other drugs, while pravastatin and rosuvastatin are the least common.

- Co-administration of clarithromycin (CYP3A4 inhibitor)

with vasodilatory calcium channel blockers, such as amlodipine and felodipine, may cause hypotension and acute renal failure. A potential lethal combination is the concomitant use of clarithromycin and colchicine, which may impair the elimination of colchicine leading to prolonged drug exposure and toxicity.

- Concomitant use of trimethoprim (sulfamethoxazole and ACE inhibitors) or angiotensin receptor blockers may increase serum potassium to life-threatening levels, including sudden death in patients.

- Interaction between NSAIDs and antihypertensive drugs. NSAIDs block the enzymes cyclooxygenase COX-1 and COX-2, which disrupt prostaglandin synthesis. Inhibition of prostaglandins in turn increases arterial smooth muscle tone and has a dose-dependent effect on natriuresis, leading to fluid retention. Through these mechanisms, NSAIDs may reduce the effectiveness of some of the most commonly used antihypertensive agents (diuretics, ACE inhibitors and angiotensin receptor blockers) and worsen patient hypertension. Concomitant use of NSAIDs with antihypertensive drugs also leads to an increased risk of acute renal failure. The strongest effects on blood pressure are indomethacin, piroxicam and naproxen. NSAIDs that have an intermediate effect on blood pressure include ibuprofen, rofecoxib and celecoxib.

- The combined use of opioids and benzodiazepines is often fatal. Studies suggest that BPD may play a role in 80% of involuntary deaths from opioid overdose, mainly due to respiratory depression. Benzodiazepines have mild respiratory depressant effects, but increase and / or prolong these opioid effects.

The symptoms of combined drug intoxication may vary depending on which drugs are taken. The management of this type of intoxication depends on the specific poison (s), the existing and predicted severity of the disease and the elapsed time between exposure and presentation.

The treatment follows the following basic steps:

- diagnostic assessment of respiration, airway, vital signs, mental state, pupil size and skin temperature and humidity, electrocardiography, blood tests and stabilization,

- maintenance care, gastrointestinal decontamination,

- antidote therapy

- extracorporeal methods (hemodialysis, charcoal haemoperfusion, continuous venous haemofiltration and exchange transfusion).

Cardiovascular drugs

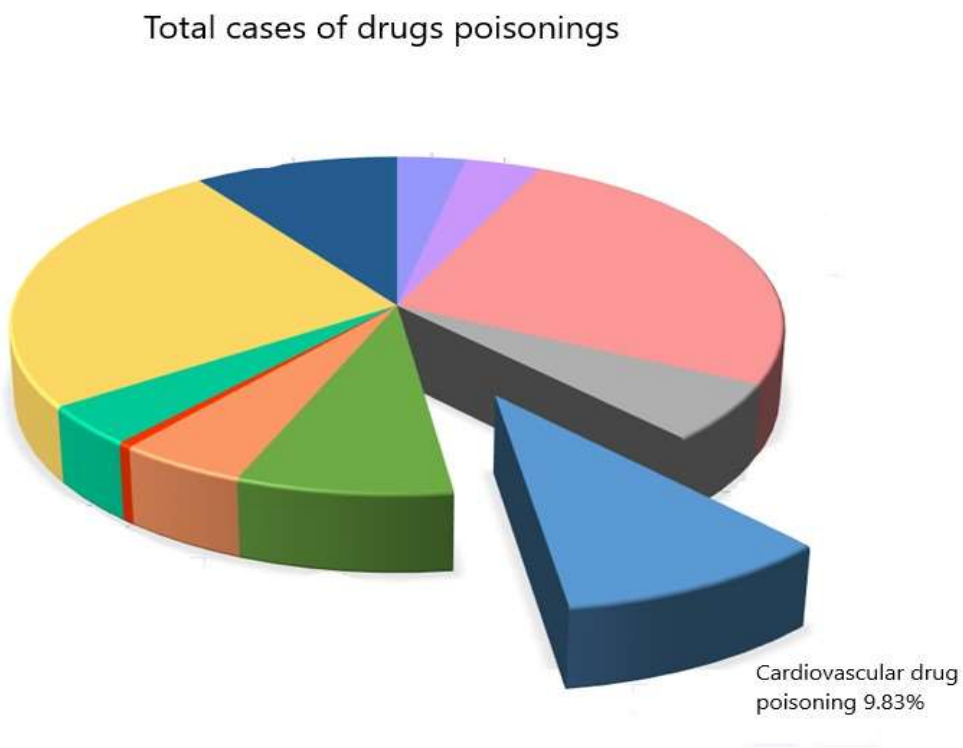

FIG. 11 Percentage of intoxications with drugs acting on SSC in relation to all ADIs

Based on data from the European System for Health Interviews (EHIS), 3 out of 10 people in Bulgaria live with hypertension. For our country, deaths from cardiovascular disease remain the leading cause of death for both women and men.

Cardiovascular overdose is associated with significant morbidity and mortality. The third group of drugs are precisely the drugs acting on the cardiovascular system - 9.83% of all drug poisonings.

The incidence of cardiovascular poisoning worldwide varies - as follows 1% of poisonings in a study from Mashhad, Iran, 6% in a study from the United States. In a study from Oslo (Norway), cardiovascular drugs caused 3% of all poisonings in adults 8.6% of all poisonings in adults in Ekaterinburg in 2009 to 2010 / 85.86 /. In the presented study, poisonings with drugs acting on the cardiovascular system represent 9.83% of all ADIs in the Varna region.

Table 2. Medicinal products acting on the cardiovascular system, known on the Bulgarian market

I. Cardiotonic drugs (T46.0)	• Digoxin Sopharma 0.25 mg tablets x 20 • Digoxin Sopharma 0.25 mg / ml solution for injection / infusion - 2ml x 10 • Lanitop 0.1 mg tablets x 30
II. Calcium channel blockers (T46.1)	• Phenylalkylamine derivatives (verapamil) Isocor, Isoptin, Verapamil - in different dosage units and dosage forms - injectable solutions, prolonged-release tablets, film-coated tablets • 1,4-Dihydropyridine derivatives (amlodipine, nifedipine, felodipine) Axel, Agen, Amlodipine, Amlovask, Amlodigama, Nordipin, Norvaski, Tenox, Corinfar, Kordaflex, Auronal, Corinker, Felohexal, Plendil, etc. - in different dosage units and dosage forms - prolonged-release tablets, film-coated tablets • Benzodiazepine derivatives (diltiazem) Aldizem, Diltiazem - in different dosage units
III. Other antiarrhythmics, not elsewhere classified (T46.2)	• Class I antiarrhythmic drugs (lidocaine, propafenone) - Lidocaine Sopharma 10 mg / ml solution for injection - 10 ml x 50 - Propastad, Rhythmonorm, Rhythmocard tablets 150/300 mg • Class III antiarrhythmic drugs (amiodarone) - Cordarone 150 mg / 3 ml solution for injection x 6 - Cordarone 200 mg tablets x 30
IV. Coronary vasodilators, not elsewhere classified (T46.3)	● Dipyridamole Antistenocardin 25 mg coated tablets x 60
V. Angiotensin-converting enzyme inhibitors (T 46.4)	● Enalapril Berlipril, Enalapril, Enahexal, Enap, Laprilen, Renapril, Renitek, Vasoprene - in different dosage units and combinations ● Perindopril Prenesa, Prestarium, Stopres - in different dosage units and combinations • Lisinopril

		Cordaker, Lisinopril, Linipril, Skopril, Vitopril - in different dosage units and combinations. • Trandolapril Gopten 0.5 mg hard capsules x 20 ➢ Angiotensin-II receptor antagonists (sartans) ● Losartan Lorista, Lozap - in different dosage units and combinations. ● Valsartan Diovan, Sarteg, Sartoval, Valsacor, Valtensin, Valsavil - in different dosage units and combinations. ● Irbesartan Irbek, Irbeso, Irbesan 150/300 mg - as a single product and in combination ● Candesartan Atakand, Candecard, Cantab, Rapido - in different dosage units ● Telmisartan Aktelsar, Tanidon, Telsart - in different dosage units and combinations ● Olmesartan Olmesta, Tensar - in different dosage units and combinations
VI.	Other antihypertensive agents, not elsewhere classified (T46.5)	● Clonidine Chlofazolin 150 micrograms tablets x 50 Chlofazolin 150 micrograms / ml solution for injection

VII. Antihyperlipidemic and antiatherosclerotic agents (T46.6)	A. HMG-CoA reductase inhibitors (statins) ● Atorvastatin Aragil, Atoris, Atorvin, Sortis, Torvacard - in different dosage units and combinations ● Lovastatin Choletar 20 mg tablets x 30 ● Simvastatin Actalipid, Neosimva, Simvastatin, Vasilip, Zokor, Simvakor - in different dosage units and combinations ● Rosuvastatin Crestor, Romazik, Rossta, Rosucard, Rosvera, Zaranta - in different dosage units and combinations B. Fibrates ● Fenofibrate Fibranor, Lipantil 160 mg film-coated tablets B. Cholesterol absorption inhibitor (ezetimibe) Ezen 10 mg tablets x 30
VIII. Peripheral vasodilators (T46.7)	A. Direct peripheral vasodilators Agapurin, Pentili, Vasonit, Nergolin, Sermion, Cavinton, Vicetin, Duzodril, Duzopharm, Cinnarizine, Sibelium - in different dosage units, combinations and dosage forms - injectable solutions, coated tablets, hard tablets, capsules C. Phytopreparations donors of NO - contain Ginkgo Biloba extract ● Tanakan 40 mg film-coated tablets x 20 ● Tebocan 120 mg film-coated tablets x 30 C. selective α1-blockers (doxazosin) Cardura, Soxon, Doxazosin - in different dosage units
IX. Antivaricose agents, including sclerosing agents (T46.8)	● Diosmin and hesperidin Detralex 500 mg film-coated tablets x 30 x 60 x 90 ● Standardized medicinal product in terms of procyanodol oligomer content Endothelon 150 mg gastro-resistant tablets x 2

X. β -adrenoceptor antagonists (T44.7)	A. Nonselective beta - blockers - Propranolol Actavis 20 mg tablets x 50 - Darob 160 mg tablets x 20 - Sotagamma 80 mg tablets x 20 - Sotahexal 80 mg tablets x 20 B. Selective beta - blockers • Beta-blockade, Betaloc, Egiloc, Metostad, Metoprolol 50/100 mg prolonged-release tablets • Atenolol-Tchaikapharma 50mg tablets x 30 • Biprol, Bizor, Bisogamma, Concor, Blockbis, Bivolet, Bravilol - in different dosage units and combinations Nebicard, Nebilet, Nebivolol 5 mg

Cardiovascular drugs are defined as drugs prescribed to treat arterial hypertension, cardiac dysrhythmias, cardiac ischemia and heart failure. The representatives of these drugs are from different pharmacological groups (Table 2). A significant part of them are prescribed and dispensed for home treatment of chronically ill, health insured patients and are subject to full or partial payment by the NHIF.

The most significant in terms of acute drug poisoning are drugs from the group of beta-blockers, calcium channel blockers, digoxin, angiotensin converting enzyme inhibitors, clonidine (centrally acting alpha2-agonist).

Combinations of drugs and alcohol

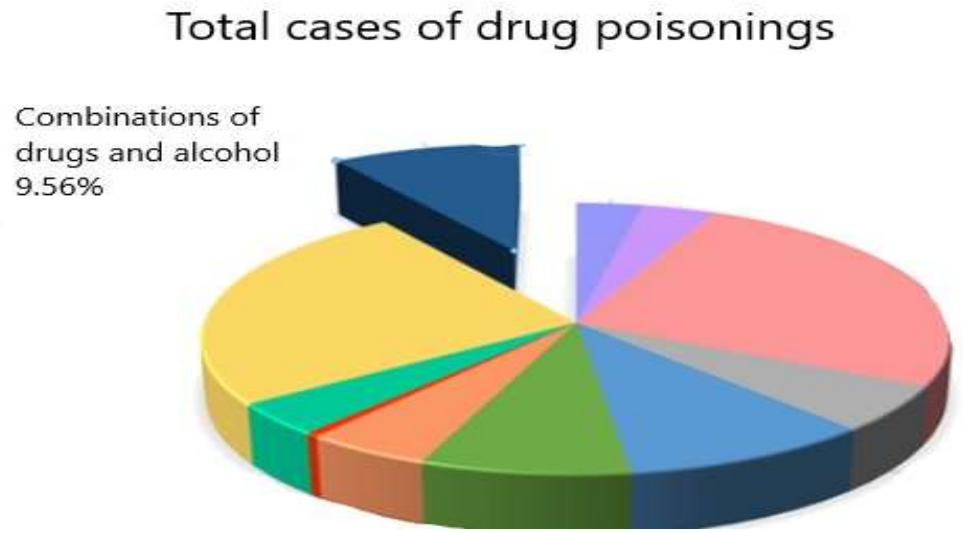

FIG. 12 Percentage of combined drug intoxications with alcohol compared to all ADIs

According to the WHO, the continent of Europe has the highest relative share in the world of deteriorating health and premature death due to alcohol use. Alcohol consumption in Europe is the highest - about 15 liters per person per year in the Czech Republic, Lithuania and Moldova. Western European countries - including Germany, France, Portugal, Ireland and Belgium - with about 12 to 14 liters. The average values for Bulgaria are 12.7 liters of pure alcohol for persons over 15 years of age. After retrospective analysis, 3803 hospitalized patients with alcohol poisoning for the period 1991-2015 were reported for the Varna region in the Clinic "Intensive treatment of acute poisoning and toxicoallergies" at the Varna Hospital at the Military Medical Academy, 94% of which were ethanol.

The use of over-the-counter or over-the-counter medications as well as herbal supplements is also extremely common. As the incidence of chronic diseases increases with age, the elderly population is particularly likely to take prescription drugs - often up to 10 per day - many of which are likely to interact adversely with alcohol. In the presented study, a fourth group among the etiological causes of acute drug poisoning. - 9.56%.

In some cases, these interactions may reduce the effectiveness of drugs or interrupt their action, and in others they may increase the toxicity to the body.

The most common combinations of LP with alcohol are characterized by the following possible reactions:

- Antihistamines (Loratidine, Desloratidine, Chlorpheniramine, Cetirizine) - Drowsiness, dizziness; increased risk of overdose

- Antistenocardial LP (Isosorbide, nitroglycerin) -tachycardia, sudden changes in blood pressure, dizziness, seizures

- Anticonvulsants, anxiolytics, antiepileptics and benzodiazepines (Lorazepam, Clonazepam, Paroxetine, Alprazolam, Valproic acid, etc.) - Potentially lethal combinations due to the additive effect of the representatives and exacerbation of depression on the CNS. Symptoms of combined use may include: drowsiness, dizziness; increased risk of overdose; slow or difficult breathing; impaired motor control; unusual behavior; memory problems; anxiety; loss of appetite; disorder; joint or muscle pain; depression; liver damage

- NSAIDs (Celecoxib, Naproxen, Diclofenac, Ibuprofen, Acetaminophen) - Ulcers, gastric bleeding, liver damage, tachycardia

- LP, used to treat a disorder with hyperactivity and attention deficit and narcolepsy (Dextro-amphetamine, Methylphenidate) - Dizziness, drowsiness, impaired concentration possible increased risk of heart problems; liver damage

- Antitussive drugs containing dextromethorpane, guaifenesin - Drowsiness, dizziness; increased risk of overdose

- Antidepressants containing aripiprazone, clomipramine, citalopram, clozapine, duloxetine, venlafaxine, fluvoxamine, risperidone, olanzapine - Drowsiness, dizziness; increased risk of overdose; increased feeling of depression or hopelessness, impaired motor control; liver damage.

- Oral antidiabetic drugs containing metformin, glipizide, glyburide - low blood sugar, nausea, vomiting, headache, rapid heartbeat, sudden changes in blood pressure; symptoms of weakness may occur

- LP used in benign prostate enlargement containing doxazosin, tamsulosin, terazosin, prazosin - Dizziness, fatigue, seizures

- LP, acting on the digestive system - Metoclopramide, Ranitidine, Famotidine - Accelerated heartbeat; enhancing the effects of alcohol; sudden changes in blood pressure (metoclopramide)

- Antihypertensive drugs - Quinapril, Verapamil, Hydrochlorothiazide, Clonidine, Amlodipine, Lisinopril, etc. - dizziness, seizures, drowsiness; arrhythmias

- Antihyperlipidemic - Lovastatin, Rosuvastatin, Atorvastatin, Simvastatin - increased risk of liver damage, gastric bleeding

Neuroleptics (antipsychotics)

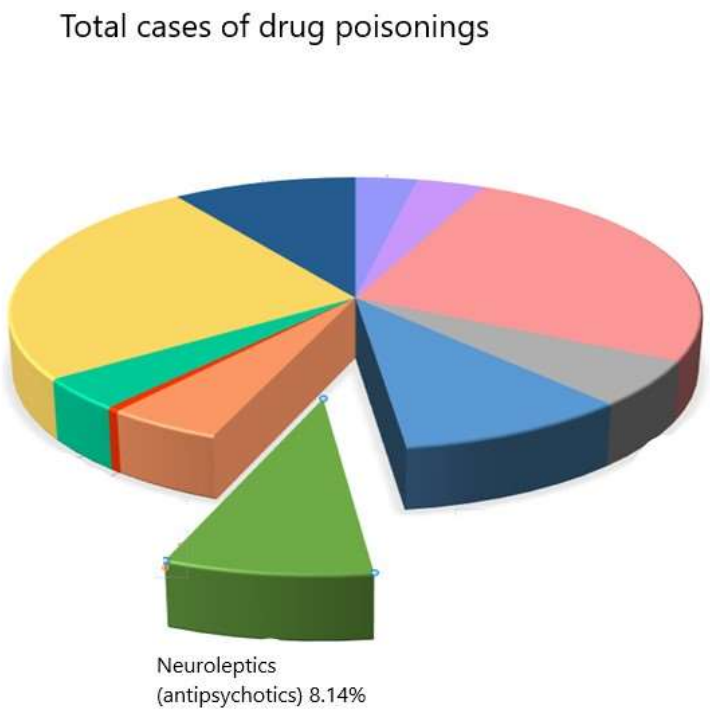

Fig.13 Percentage of neuroleptic poisonings in relation to all ADIs

They are used to treat and manage the symptoms of many mental disorders (psychosis, bipolar disorder) as well as other emotional and mental disorders, including hallucinations, delusions or mania symptoms, and are also used as sedatives, tranquilizers, antiemetics, to control hiccups and to treatment of drug psychosis. 8.14% is the relative share of acute neuroleptic poisonings in the Varna region.

Overview of the antipsychotics available in the commercial network of Bulgaria, conditionally divided into generations:

I generation - butyrophenones: Haloperidol (Haloperidol - Sopharma, Haloperidol - Richter)

- Phenothiazines

Chlorpromazine (Chlorpromazine Sopharma), Thioridazine, Fluphenazine (Moditen Depot).

Generation II - Dibenzodiazepines:

Clozapine (Leponex, Xenopalan, Xenopal), Risperidone (Rispolux, Speridan, Medorisper), Quetiapine (Hedonine, Kvelux, Tevaquel, Centroquin), Olanzapine (Olanzapine Actavis, Olanzapine Accord, Elanzapine)

- Quinolines - Aripiprazole (Abilifay)

- Benzisoxazole - Risperidone (Medorisper, Neorisp, Risperidone, Speridan, etc.)

The toxicity of antipsychotic drugs can be increased by co-administration of other agents, in particular drugs with similar metabolic pathways. Combinations between neuroleptics and tricyclic antidepressants, benzodiazepines, or lithium are common, leading to the need for appropriate toxicological screening for these substances. Mortality is relatively rare in overdose, but in NMS, mortality can reach 10-12%.

Patients with acute neuroleptic overdose have a wide range of reactions, depending on the degree of mental disorder, age, usual use of drugs and individual sensitivity - movement disorders, hypotension and dysrhythmias, orthostatic dizziness or generalized weakness. ECG findings include prolongation of QT, PR and QRS intervals, and others. The diagnosis of neuroleptic malignant syndrome requires urgent action.

Poisoning with other drugs

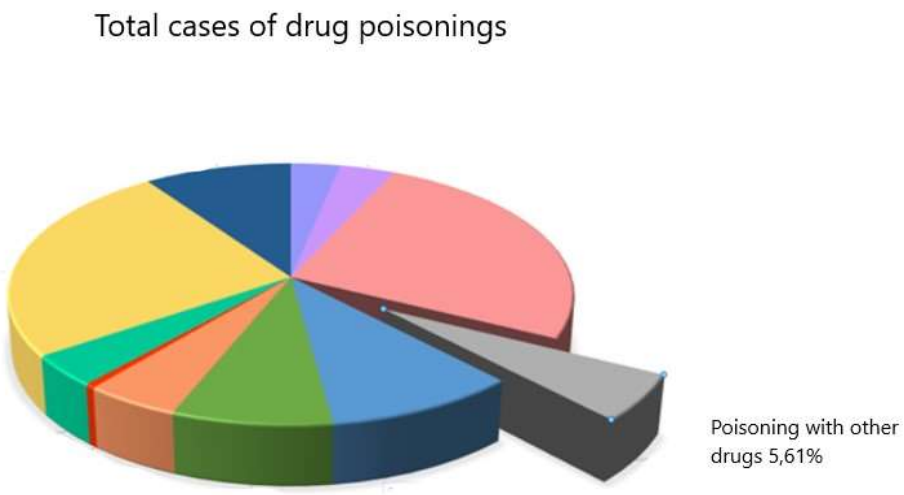

Fig.14 Percentage of poisonings with other drugs in relation to all AMI

This group includes over-the-counter drugs (OTC - antitussive, antidiarrheal, antihistamine, iron supplements, laxatives, vitamin preparations), antibacterial and other products. Due to the great variety of representatives, poisoning with them is often attributed to intoxications with combinations of drugs. 5.61% of all drug intoxications over the 30-year period are caused by other drugs.

OTC drugs are designed to treat various symptoms such as pain, cough and colds, diarrhea, heartburn, constipation, acne and others without the need for a doctor's prescription. Their use carries the risk of developing characteristic or serious side effects depending on the dose taken, as well as problematic drug interactions.

Non-steroidal anti-inflammatory, non-opioid analgesics and antipyretics

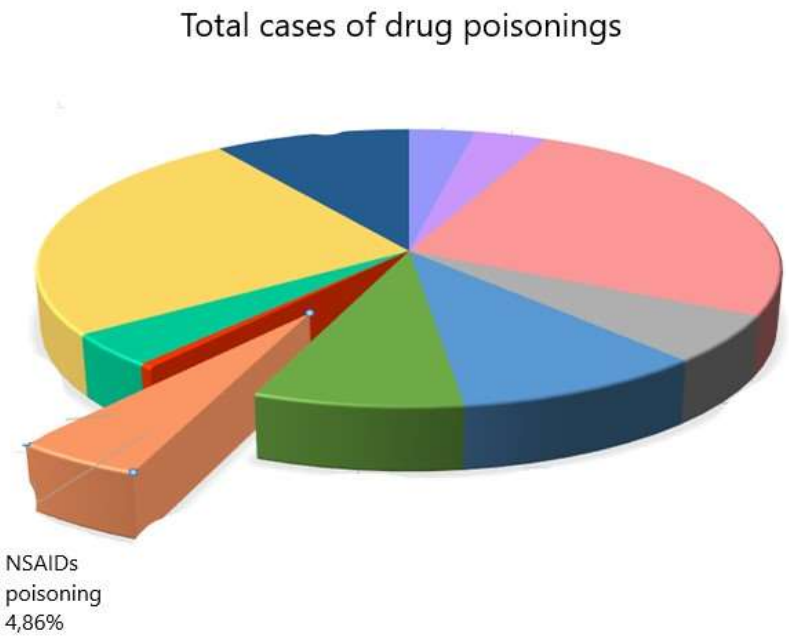

FIG. 15 Percentage of NSAID intoxications compared to all ADIs

Non-steroidal anti-inflammatory drugs (NSAIDs) are characterized by anti-inflammatory, analgesic, antipyretic effects, and are also widely used in chronic diseases, significantly reducing the quality of life, performance and social activity of patients.

The use of NSAIDs worldwide is targeted at a wide range of diseases and pathological conditions, such as

- Diseases of the musculoskeletal system - osteoarthritis, non-specific back pain, rheumatoid arthritis, spondyloarthritis, gout and other metabolic arthropathies, local inflammation of the soft tissues of rheumatic nature (tendinitis, tendovaginitis bursitis) and many others;

- Injuries and other conditions accompanied by pain caused by injury or acute inflammation, including dental disease;

- Postoperative pain;

- Renal and biliary colic;

- Headache and migraine;

- Oncological diseases (as a component of palliative analgesic therapy);

- Gynecological diseases, dysmenorrhea

Reports indicate that sales of NSAIDs, which are dispensed with or without a doctor's prescription in various forms - capsules, tablets, syrups, etc., are approximately $ 18 billion a year. Nonsteroidal

anti-inflammatory, non-opioid analgesics and antipyretics are the most commonly prescribed drugs. In Bulgaria there are over 180 trade names of NSAIDs (as monoproducts or in various combinations, doses and pharmaceutical forms), registered as OTC or LP, prescribed by a doctor. The percentage of poisonings with this large group is 4.86% for the discussion period.

Table 3 NSAIDs known on the Bulgarian market

Group	Subgroup	Representatives	Clinical symptoms of poisoning
Acid derivatives	Salicylic acid Maximum Daily dose - 1500 mg	Acetylsalicylic acid ● Acard, Acesal Protect, Acetizal, Apiri, Aspetin, Aspirin Ultra, Ruvexin	Observed hyperventilation, tachycardia, diaphoresis, tinnitus, disorientation, stupor, coma, cardiovascular or pulmonary arrest and lethal outcome at doses above 15 g
	Acetic acid	Diclofenac • Diklak 75/150 mg modified-release tablets x 50 • Diclofenac Duo 75 mg prolonged-release hard capsules, Naclofen Duo, • Voltaren Retard 100 mg Indomethacin ● Indomethacin Sopharma 25 mg gastro-resistant tablets x 30 Aceclofenac Aflamil 100 mg film-coated tablets and powder for oral suspension x 20	Indomethacin poisoning can cause headache, lethargy, disorientation, seizures, nausea, vomiting, and gastrointestinal bleeding. Diclofenac may cause nausea, vomiting, tinnitus, hallucinations and acute renal failure.
	Propionic acid	Ibuprofen • BlockMAX, Brufen, Doloren, Flexistad 400/600 mg, Ibalgin Rapid, Ibuprofen Polfa, Ibuprom	Headache, tinnitus, drowsiness, nausea, vomiting and abdominal pain are the most

			max, Mig - 400, Nurofen 200 mg / 400, Oklis 400 mg granules for oral solution in sachet x 10 Ketoprofen • Bi-Profenid 150 mg modified-release tablets Ketonal 100 mg / 2 ml solution for injection, granules for oral solution, capsules • Profenid 100 mg powder and solvent for solution for injection • Profenid LP 200 mg prolonged-release tablets Naproxen Nalgesin 275/550 mg film-coated tablets	common symptoms and usually occur within 4 hours after taking ibuprofen. Ingestion of more than 400 mg / kg ibuprofen has been associated with seizures, apnea, hypotension, bradycardia, metabolic acidosis, and renal and hepatic dysfunction.
	Pyrazolone derivatives		Metamizole • Algozone, Analgin, Analgin Hin, Generalgin, Hexalgin, Proalgin, Dialgin 500/1000 mg tablets, oral drops, effervescent powder	Hypotension and arrhythmia, bronchospasm, especially in patients with asthma, maculopapular rash, nausea, vomiting, abdominal pain region, diarrhea, anxiety, agitation, dizziness, drowsiness, convulsions, coma
	Oxicams		Piroxicam ● Flamexin 20 mg powder for oral solution and tablets ● Piroxicam Sopharma	Sometimes these NSAIDs can cause dizziness, blurred vision, seizures and

		Meloxicam ● Melbek 7.5 / 15 mg, Melox 15 mg, Trosicam 7.5 / 15mg, orodispersible tablets Lornoxicam Xefo Rapid 8 mg film-coated tablets x 10	coma.
Non-acid derivatives	Sulfonaniline derivatives	Nimesolid ● Alden 100 mg effervescent tablets Aulin 100 mg granules for oral suspension and tablets, Enetra, Nimesil 100 mg granules for oral suspension x 15	Lethargy, drowsiness, nausea, epigastric pain and possible gastrointestinal bleeding. Hypertension, acute renal failure, respiratory depression, coma are rare.
	Coxibs	Celecoxib ● Aclexa, Celebrex Definax 100/200 mg hard capsules Etoricoxib ● Arkoxia 30/60/90/120 mg film-coated tablets x 7 ● COXIENT 30/60/90/120 ● Costarox 30/60/90/120 Etoristad 30/60/90/120 mg	They are considered relatively safe

Sedative-hypnotic drugs

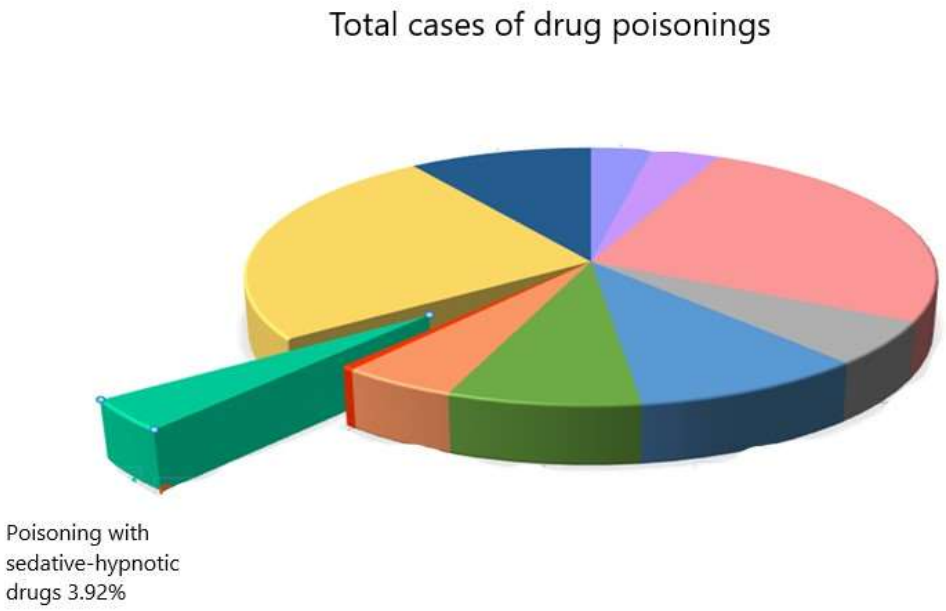

Fig.16 Percentage of poisonings with sedative-hypnotic medicinal products in relation to all ADIs

The group of sedative-hypnotic drugs is characterized by heterogeneity in terms of toxicokinetics of the representatives, the characteristics of the pharmaco- and toxicodynamics, the clinical manifestations of poisoning.

Other etiological causes of acute poisoning are sedative-hypnotic drugs - 3.92%. For this reason, there is a difference in approaches to treating patients with acute poisoning. Sedative-hypnotic drugs can be classified according to the type and duration of their action:

❖ Barbiturate derivatives -

- with ultra-short action - Thiopental (Thiopental 1 g powder for solution for injection)

- With short and intermediate action - Amobarbital, Pentobarbital

- Long acting - Phenobarbital (Phenobarbital 100 mg / ml solution for injection, Belergamine 0.1 mg / 0.3 mg / 20 mg coated tablets x 20 - combination medicine)

❖ Non-barbiturate sedative-hypnotic-

- Zopiclone - (Zopiclone-Takeda 7.5 mg film-coated tablets x 10; Ecodorm 7.5 mg film-coated tablets x 10)

- Benzodiazepines - their toxicity was discussed in the previous section

- Antihistamines (over-the-counter sleep aids) - Dimenhydrinate 50 mg tablets x 30; Womakur 40 mg suppositories, Kalmaben tab. X 20

- Melatonin - an agonist of melatonin receptors. It exists as a dietary supplement in single form of 1-10 mg or in combination with other various ingredients.

Frequent prescribing of these drugs for insomnia and other disorders increases the risk of accidental overdose or suicide alone or in combination with other substances.

Anticonvulsant drugs

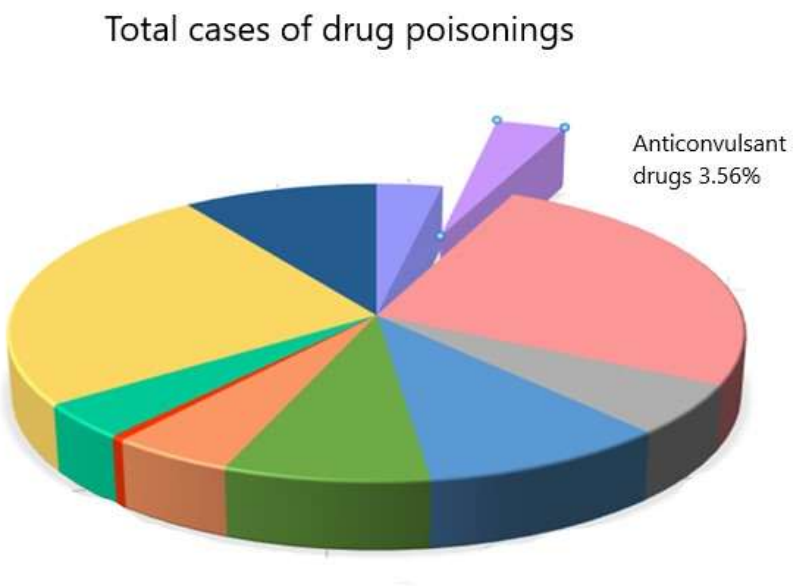

FIG. 17 Percentage of anticonvulsant drug intoxications compared to all ADIs

In our study, 3.56% of acute poisonings were caused by members of this group

Types of antiepileptic drugs: (Table 4)

1. Barbiturates and derivatives

- Phenobarbital (Phenobarbital 100 mg / ml solution for injection / drug combination - Sedalgin neo tab.)

2. Carboxamides

- carbamazepine (Finlepsin tablet 200 mg, Neurotop tablet 200 mg, Neurotop retard tablet 300, Neurotop retard tablet 600 mg)

- oxcarbazepine (Tevaleptin tablet 300 mg, tevaleptin tablet 600 mg, Trileptal susp. 60 mg / ml, Trileptal 300 mg, trileptal 600 mg)

3. Hydantoins

- phenytoin (Epilane -D 100 mg. Table)

4. Succinimides

- Ethosuximide (Petinimide caps. 250 mg)

5. GABA-transaminase inhibitors

- valproic acid (Convulex caps. 300 mg, Convulex syrup 50 mg / ml, Convulex chrono 300 mg prolonged-release tablets, Convulex chrono 500 mg prolonged-release tablets, Depakine 500 mg gastro-resistant tablets, Depakine 57.64 mg / ml syrup, Depakine chrono 500 mg prolonged-release tablets, Depakine chrono 300 mg prolonged-release tablets)

6. Inhibitors of presynaptic absorption of GABA

- Tiagabine (Gabitril 10 mg film-coated tablets)

7. GABA protectors

- Topiramate (Talopam 100 mg film-coated tablets, Talopam 50 mg film-coated tablets, Topilex 50 mg film-coated tablets, Topilex 100 mg film-coated tablets)

8. Antiepileptic drugs with different structure and mechanism

- Lamotrigine (Epitrizine 100 mg tablets, Epitrigine 50 mg tablets, Lamotrix 25/50/100/200 mg tablets, Lamictal 5/25/50/100 mg tablets)

- Gabapentin (Gabagamma 100/300/400/600 mg hard capsules, Gabaneural 100/300/400 mg hard capsules, Neurontin 300/400 mg capsules)

- Levetiracetam (Levebon 500/1000 mg film-coated tablets, Levetiracetam Accord tablets 500/1000 mg, Levetiracetam Herds tablets 500/1000 mg, Noepix tablets 500/1000 mg)

- Pregabalin (Lyrica caps. 75 mg, Pregabin caps. 75 mg, Pregabalin Sandoz caps. 75 mg, Pregabalin Mylan caps. 75 mg)

Carbamazepine and sodium valproate are among the most widely used by the older generation. Phenobarbital is more commonly used in Asia. A study shows that levothiracetam is the most widely used anticonvulsant, including in children in the United States.

Table. 4 Most commonly used anticonvulsants and their potential toxic effects

Medicinal substance	Toxic effect
1. Gabapentin	Drowsiness, dizziness, ataxia, mild tremor, slurred speech, diplopia, tachycardia, hypotension or hypertension; diarrhea
2. Lamotrigine	Lethargy, dizziness, ataxia, stupor, nystagmus, hypertension, seizures; QRS prolongation, nausea and vomiting, hypokalaemia, hypersensitivity: fever, rash (Stevens-Johnson syndrome) hepatitis, renal failure
3. Levetiracetam	Drowsiness, agitation, aggression, depressed level of consciousness, respiratory depression and coma
4. Tiagabine	Drowsiness, confusion, agitation, dizziness, ataxia, depression, weakness, tremor, seizures
5. Topiramate	Convulsions, drowsiness, speech impairment, blurred vision, diplopia, lethargy, impaired coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression
6. Valproic acid	Vomiting, giving, confusion, unconsciousness Shivering, decreased consciousness, Respiratory depression, Hypotension, Hypoglycaemia, electrolyte disturbances
7. Carbamazepine	Drowsiness, slurred speech, ataxia, hallucinations, nausea, vomiting, bullous skin, tremor, seizures, oliguria

Antidepressants

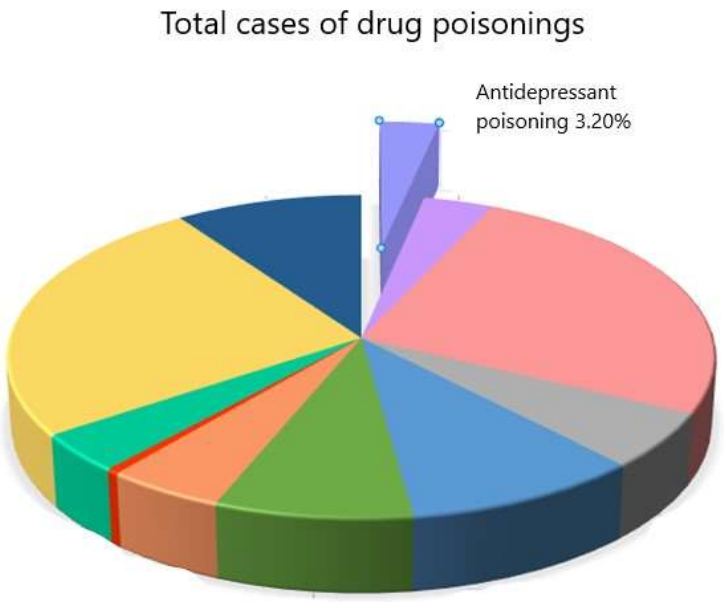

Fig.18 Percentage of antidepressant poisonings in relation to all ADIs

Since their introduction in the 1950s, antidepressants have been used primarily to treat depression, as well as many other conditions, such as panic disorder, anxiety, post-traumatic stress disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and social phobia. , fibromyalgia, nocturnal eating syndrome, menopause, migraine prevention.

On the other hand, antidepressants are one of the most commonly used medications in self-poisoning. The representatives used for this purpose may differ from country to country. For the Varna region 3.20% are poisonings with this type of medicinal products.

Each type (class) of antidepressant affects the neurotransmitters serotonin, norepinephrine and dopamine in different ways:

- Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine (Biflox 20 mg hard capsules x 28)

Paroxetine (Seroxate 20 mg film-coated tablets x 30; Xetanor 20 mg film-coated tablets x 30; Paroxat film-coated tablets 20 mg x 30)

Sertraline (Zoloft 50 mg film-coated tablets x 28; Stimuloton 100 mg film-coated tablets x 28; Setaloft 50 mg film-coated tablets x 30)

Citalopram (Seropram 20 mg film-coated tablets x 28; Oropram 20 mg film-coated tablets x 28)

Escitalopram (Cipralex 10 mg film-coated tablets x 28; Escitacon 10 mg film-coated tablets; Elicea 10 mg film-coated tablets x30; Escitil 10 mg film-coated tablets x 30; Escitil 20 mg film-coated tablets x 30; Esobel 10 mg film-coated tablets x 28; Esobel 20 mg film-coated tablets x 28)

- Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Duloxetine (Aritavi 30/60 mg gastro-resistant capsules, hard 28; Dulodet 30/60 mg hard gastro-resistant capsules x 28; Duloxy 30/60 mg gastro-resistant hard capsules x 28; Dulsevia 30/60 mg gastro-resistant hard capsules x 28; capsules x 28; Duxet 30/60 mg capsules gastro-resistant hard capsules x 28;

Venlafaxine (Effectin EP 150 mg prolonged-release capsules, hard x 28; Effectin EP 75 mg prolonged-release capsules, hard x 28; Laroxin SR 150 mg prolonged-release hard capsules x 28; Laroxin SR 75 mg prolonged-release hard capsules x 28; Velaxin 75/150 mg prolonged-release hard capsules x 28; Tifaxin MR 150 mg prolonged-release capsules, hard x 28; Tifaxin MR 75 mg prolonged-release capsules, hard x 28)

- Atypical antidepressants

Trazodone (Tritico 150 mg prolonged-release tablets x 30; Tritico 75 mg prolonged-release tablets x 30; Tritico XR 150 mg prolonged-release tablets x 28)

Mirtazapine (Remirta 30 mg film-coated tablets x 30)

Bupropion (Maisimba - in combination with naltrexone hydrochloride)

- Tricyclic antidepressants (TCAs)

Amitriptyline (Amitriptyline 25 mg coated tablets x 30)

Clomipramine (Anafranil 10 mg coated tablets x 30; Anafranil 25 mg coated tablets x 30)

- Monoamine oxidase (MAO) inhibitors

Selegeline (Yamax 5 mg tablets x 30)

Moclobemide (Aurorix 150 mg film-coated tablets x 30

Opioid analgesics

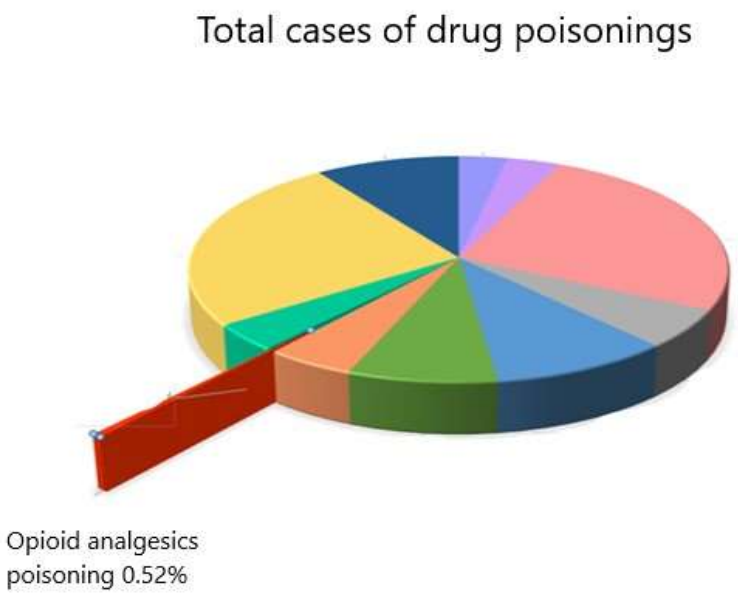

Fig.19 Percentage of opiate poisonings in relation to all ADIs

Intoxication with opioid analgesics is the least numerous - 0.52%.

Opioid analgesics include natural alkaloids (morphine, codeine) and synthetic compounds (trimeperidine, fentanyl, tramadol, nalbuphine, etc.). Most synthetic preparations are obtained on the principle of modifying a morphine molecule, while preserving the elements of its structure. Chemical modification of the morphine molecule also produces substances that are its antagonists (naloxone, naltrexone). Natural alkaloids are extracted from opium. Pure opium is a mixture of alkaloids extracted from the juice of the fruit of Papaver somniferum (poppy), which has a spherical multi-nested shape. The term 'opiate' is often used to refer to synthetic and semi-synthetic derivatives.

Opioid analgesics have been used for centuries because of their analgesic effect in the treatment of acute and chronic pain, trauma, post-traumatic shock, acute myocardial infarction, anesthesia, diarrhea and more. They act on opioid receptors (mu-, kappa- and delta-) located in the spinal cord, trunk, limbic system, thalamus, and others. Their physiological role is related to the synthesis of endogenous opioids - endorphins, enkephalins and dinorphins, which reduce pain, improve mood and more. Stimulation of G-protein-coupled receptors inactivates adenylate cyclase, reduces calcium ion influx, and ultimately inhibits the release of a mediator from the presynaptic membrane. (table 21)

Table 5. Medicinal products containing opioids according to the strength of agonist action and chemical structure

Mild to moderate agonists	Phenanthrene Codeine phosphate hemihydrate (Sedalgin neo - combined preparation: Codeine phosphate hemihydrate 10 mg, Caffeine, Paracetamol, Metamizole, phenobarbital, available with a green prescription and Solpadein - Codeine phosphate hemihydrate (Paracetamol - 8 mg, doctor) Oxycodone (Oxycodone Actavis Caps. 10/20 mg, Oxycodone Actavis Extended Release Table 10/20/40 mg, Oxycontin Tablet 10 mg - available with a yellow prescription) Loperamide (Diarostad 2 mg hard capsules, Imodium 2 mg hard capsules, Imodium instant 2 mg orodispersible tablets, Lopedium 2 mg hard capsules, Stoperan 2 mg hard capsules, Vacontil 2 mg capsules, Imomed 2 mg hard capsules - OC products)
Opioids with mixed receptor action	Phenanthrene Nalbuphine Buprenophrine (Buprenorphine Actavis 35 / 52.5 / 70 micrograms / hour transdermal patch, Buprenorphine Sandoz 35 / 52.5 / 70 micrograms / hour transdermal patch - available with a green prescription)

Diagnosis of acute drug poisoning

The diagnosis of acute poisoning is performed immediately, thoroughly and comprehensively, using the means of paraclinical, clinical, toxicological, instrumental and laboratory tests. The detailed anamnesis and physical examination are of great importance for establishing and determining the type of poisoning.

Table 6. General toxicodromes and typical causes

Anticholinergic	agitation, hallucinations, delirium with murmuring speech, coma, mydriasis, hyperthermia, tachycardia, hypertension, tachypnea, dry red skin, dry mucous membranes, reduced bowel sounds, urinary retention, myoclonus, choreoathetosis, behavior	Antihistamines, tricyclic antidepressants, antiparkinsonian agents, antispasmodics, phenothiazines, atropine
Cholinergic	disorientation, coma, miosis, bradycardia, hypertension or hypotension, tachypnea or bradypnea, increased salivation, urinary and fecal incontinence, diarrhea, vomiting, diaphoresis, lacrimation, gastrointestinal spasms, bronchoconstriction, muscle	physostigmine, neostigmine, donepezil, pilocarpine, betanechol, rivastigmine, galantamine
Sedatives / Hypnotics	CNS depression, confusion, stupor, coma, mydriasis / miosis, hypothermia, bradycardia, hypotension, apnea, bradypnea, hyporeflexia	Benzodiazepines, barbiturates, carisoprodol, glutethimide, zolpidem
Sympathomimetics	Tachycardia, mydriasis, anxiety, delirium, paranoid delusions, diaphoresis; fever; seizures, tremors, hyperreflexia, seizures	Cocaine, amphetamines, ephedrine, pseudoephedrine, phenylpropanolamine, theophylline, caffeine
Opioids	CNS depression, coma, miosis, Bradypnea, characteristic apnea; possible development of hypothermia, bradycardia, hypotension, hyporeflexia, pulmonary edema, signs	Opioids (eg heroin, morphine, methadone, oxycodone, hydromorphone)

	of prick	
Salicylates	fever; tachypnea, tinnitus, lethargy, altered mental status, respiratory alkalosis, metabolic acidosis, ketosis, vomiting	Preparations containing acetylsalicylic acid
Serotonin syndrome	Confusion, agitation, coma, mydriasis, Hyperthermia, tachycardia, hypertension, tachypnea, Tremor, myoclonus, hyperreflexia, clonus, diaphoresis, flushing, trismus, rigidity, diarrhea	Fluoxetine, trazadone, meperidine, SSRIs, dextromethorphan, TCAs, L-tryptophan
Extrapyramidal	Stiffness, tremor, hyperreflexia	Haloperidol, phenothiazines, metoclopramide
Hallucinogens	Hallucinations, perceptual distortions, depersonalization, agitation, mydriasis, Hyperthermia, tachycardia, hypertension, tachypnea, nystagmus	Phencyclidine, LSD, designer amphetamines

Table 7. Specific color of urine due to the use of drugs

Amitriptyline, triamterene	Red - brown
Metronidazole, nitrofurans	Brown-red
Riboflavin, B vitamins	Yellow green
Salicylates, anticoagulants, bismuth salts	Red-black
Rifampicin	Yellow-red

Table 8. Specific skin color due to the use of drugs

Tetracycline, resorcinol	Dark blue
Amiodarone, phenothiazines, quinine, bismuth salts	Gray-blue
Imipramine, methyldopa, levodopa, phenacetin	Brown
Rifampicin	Red
Carotene, nitrazepam	Yellow

Table 9. Specific ocular changes due to the use of drugs

Miosis	Barbiturates, bezodiazepines, methyldopa, clonidine, opiates
Mydriasis	Antihistamines, amphetamines, cocaine atropine, ephedrine
Nystagmus	Barbiturates, carbamazpine, phenytoin
Diplopia	Barbiturates, opiates, phenytoin, tetracycline
Blurred vision	Anticholinergic, MAO inhibitors, lithium, methanol
Altered color vision	Digitalis, ibuprofen, nalidixic acid
Changes in the cornea	Chloroquine, vitamin D and others

Typical dermal manifestations of acute toxicity as a result of the use of certain drugs:

● Atropine - dry, hot skin

● Salicylates - profuse sweating

● Barbiturates, imipramine, methadone, nitrazepam - blisters on the skin

● Warfarin - petechiae and purple spots

● Clonidine, niacin, sympathomimetics, theophylline - redness

Careful examination of the oral cavity can provide valuable information about the etiology of poisoning in some cases.

● Glossit - trimethoprim + sulfamethoxazole, diclofenac, naproxen, metroniazole, amoxicillin, erythromycin,

● Stomatitis - cytostatic drugs, penicillamine, gold salts

● Mumps - clonidine, thioridazine

● Gum hyperplasia - phenytoin, valproate, nifedipine, diltiazem, verapamil

● Pigmentation in the oral cavity - cisplatin, oral contraceptives, antimalarial drugs

● Changes in tooth color - fluorides, tetracyclines, iron preparations

● Dental caries - vitamin syrups and cough syrups, antibiotic syrups (for chronic use)

● Xerostomia - antipsychotics, tricyclic antidepressants, antihistamines, anticholinergics, anticonvulsants, diuretics, etc.

● Hypersalivation - parasympathomimetics, iodides

Assessment of the severity of poisoning (ASP)

There is a standardized scale for grading the severity of poisonings, allowing a qualitative assessment of morbidity, better identification of real risks and comparability of data. The tool was developed by the European Association of Poison Centers and Clinical Toxicologists, the International Chemical Safety Program and the European Commission in the 1990s. TABs serve to schematically classify cases of poisoning in adults and children, regardless of the type and number of agents involved. It is possible to be modified or changed, but it serves as a basis and takes into account the overall symptoms (including subjective symptoms and objective signs) / 31,32 /. The method has a wide range of applications such as: comparison of toxicological results between substances / classes, doses and types of exposure, quantitative assessment of morbidity and risks due to poisoning, evaluation of methods of treatment and others. OTO classifies the severity of poisoning as none (0), mild (1), moderate (2), severe (3) and fatal (4). The scale includes

data from 12 different organ systems and a number of subjective variables such as 'mild haemolysis', 'mild hypotension' and 'prolonged cough', which are entered by the assessor.

Table 10. Classification of the severity of poisoning

Body organs and system	No symptoms or signs of poisoning (0)	Mild, transient and spontaneously resolved symptoms (1)	Clear or prolonged symptoms (2)	Severe or life-threatening symptoms (3)	Fatal - death (4)
GIT		Vomiting, diarrhea, pain, minimal mouth ulcers, edema	Prolonged vomiting, diarrhea, pain, ileus, dysphagia	Massive hemorrhage, perforation, severe dysphagia	
Respiratory system		Irritation, cough, shortness of breath, mild dyspnea, mild bronchospasm	Prolonged cough, bronchospasm, dyspnoea, hypoxemia, required additional oxygen	Respiratory failure, pulmonary edema, pneumonia, pneumothorax	
Nervous system		Drowsiness, dizziness, tinnitus, ataxia, mild extrapyramidal symptoms, Mild visual or auditory disturbances	Short apnea, bradypnea, Confusion, agitation, hallucinations, delirium, rare, generalized or localized seizures, Severe extrapyramidal symptoms, visual and auditory disturbances	Coma, respiratory depression, agitation, generalized seizures, status epilepticus, generalized paralysis or paralysis affecting vital functions, blindness, deafness	
Cardiovascular system		Isolated extrasystoles, Mild and transient hypo / hypertension	Sinus bradycardia / tachycardia, Frequent extrasystoles, atrial fibrillation, myocardial ischemia, More pronounced hypo / hypertension	Severe sinus bradycardia / Tachycardia, life-threatening ventricular distresses, Myocardial infarction, Shock, hypertensive crisis	
Metabolic balance		Mild acid-base disorders, Mild hypoglycaemia, Short-term hyperthermia	More pronounced acid-base disturbances, More pronounced hypoglycaemia, Hyperthermia with longer duration	Severe acid-base disorders, Severe hypoglycaemia, Dangerous hypo- or hyperthermia	
Liver		Minimal increase in serum enzymes (2-5 times above normal)	Increase in serum enzymes (5-50 times above normal), but without clinical and diagnostic data for the	Increase in serum enzymes (over 50 times normal, with biochemical and clinical evidence of liver failure	

			liver dysfunction		
Kidneys		Minimal proteinuria / hematuria	Massive proteinuria / haematuria, renal dysfunction (eg oliguria, polyuria, serum creatinine ~ 200-500 μmol / l	Renal insufficiency (eg anuria, serum creatinine from> 500 μmol / l)	
Blood		Mild hemolysis; Mild methaemoglobinaemia (metHb ~ 10-30%)	Hemolysis, More pronounced methaemoglobinaemia (metHb ~ 30-50%), Coagulation disorders without Bleeding, anemia, leukopenia, thrombocytopenia	Massive hemolysis Severe methaemoglobinaemia (metHb> 50%), Bleeding coagulation disorders, Severe anemia, leukopenia, thrombocytopenia	
Muscles		Mild pain and tenderness	Pain, stiffness, spasms and fasciculation, Rhabdomyolysis	Intense pain, extreme stiffness, extensive spasms and fasciculation Rhabdomyolysis with complications, Ward syndrome	
Skin (local effects)		Irritation, 1st degree burns (redness) or 2nd degree burns	2nd degree burns in 10-50% of the body surface or 3rd degree burns in <2% of body surface area	2nd degree burns in> 50% of the body surface or 3rd degree burns> 2% of body surface area	
Eyes (local effects)		Irritation, redness, tearing, mild swelling of the palpebral	Intense irritation, corneal abrasion, Small (punctate) corneal ulcers	Permanent injuries	

Interpretation of the data follows and specific actions are recommended:

In the first degree - mild, transient and spontaneously resolving symptoms, medical supervision of the patient is recommended. In the second degree with pronounced or prolonged symptoms - supportive care and monitoring, in the third degree with severe or life-threatening symptoms - emergency measures to ensure vital functions.

The results of the clinical severity assessment are used in critically ill patients to predict the progression of their disease in order to achieve timely, appropriate and cost-effective medical management of poisoning.

Comparison between acute drug poisoning with suicidal intent and all others

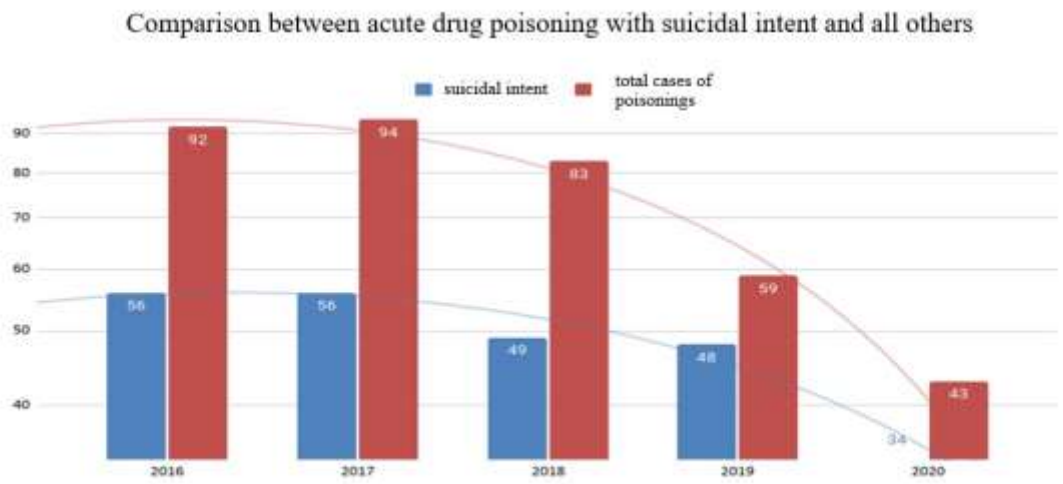

FIG. 20 Comparison between suicidal ADIs and all others

Figure 20 shows that suicide poisonings represent more than 50% of the total number of all acute intoxications for the last 5 years of the period under consideration. Intentional self-harm is a major preventable public health problem. The number of deaths as a result of intentional self-harm, including with the help of pharmaceuticals in 2020 for the Northeast region is 8.7 per 100,000 population. This raises questions related to the prevention of suicidal behavior of the population of Varna region.

Mortality due to poisoning

Mortality from poisoning varies from country to country, depending on the type of poison, the level of awareness of the poisoning, the availability of medical facilities and the presence or absence of qualified personnel. While in developed countries the mortality rate is between 1 and 2%, in other countries it varies between 15-35%. Children under the age of 15 are most often victims of accidental poisoning, which is characterized by low mortality. On the other hand, people over the age of 15 have the highest number of suicides, with high mortality. The mortality rate, due to accidental poisoning of 100,000 people in the population of Bulgaria, according to WHO data has increased from 0.45 (2018) to 0.54 (2019).

Strategies for prevention and control of acute drug poisoning

Both preventive and curative measures are applied to deal with and manage the problem of acute poisoning. Many approaches need to be applied to reduce morbidity and mortality. There are two strategies for improving public health in acute poisoning, namely individual-oriented and population-oriented.

Management decisions include assessing cases of poisoning with clinical psychometric instruments or referring intentional poisoning to a psychologist or psychiatrist, specific educational

programs for limited households or communities. Careful analysis of the patient's psychological state (depressed, unresponsive, unresponsive, agitated, anxious) allows a realistic assessment of psychosocial alternatives in terms of immediate and long-term treatment, placement and long-term follow-up or outpatient care.

Today, psychosocial assessment has become an important component in the overall assessment of patients admitted to toxicology clinics. It should be conducted in any case by interviewing companions, family members or friends, the patient himself.

The role of the pharmacist in the control of acute drug poisoning

The roles of pharmacists as medical professionals in the control of acute drug intoxications are numerous:

• Provision of toxicological information and advice, activities on toxicological vigilance, education and training in prevention and treatment of poisoning;

• Together with other medical professionals, pharmacists are involved in developing contingency plans and chemical disasters;

• Participate in the implementation of plans for monitoring the adverse effects of medicinal products;

• Update data on various toxins, the presence or absence of a specific antidote and existing treatment options;

• To participate in coordination initiatives for control and management of poisoning;

• Suicide prevention

In terms of prevention, knowledge of toxicology, pharmacology, pharmacognosy, and pharmaceutical care serve to improve patient relationships and provide a more effective and cost-effective drug supply. The organization of campaigns and the provision of materials on vaccination to problems with drug toxicity, emergency pre-medical care for poisoning, recognition of various types of poisons found in households are an essential part of the work of pharmacists.

As the most accessible medical professionals, pharmacists are often sought for information on the safety and interactions of medications taken, as well as whether or not inadvertently ingested medicinal products or supplements are potentially toxic and whether urgent treatment needs to be taken. When a patient is admitted to a toxicology clinic or emergency department, hospital pharmacists help by providing medication or antidotes for the correct drug therapy for the patient.

Follow-up care for patients is on their return home and includes monitoring whether doctors' recommendations are followed, whether there is a risk of re-ingestion, whether the environment is safe, etc.

Pharmacists, as health professionals, need to be trained in suicide prevention strategies so that they can raise their own awareness and identify referrals to at-risk individuals.

Pharmacists can help identify patients through their daily contact with patients and during formal relationships with physicians in the overall management of drug therapy.

Training for pharmacists can be structured and focused on the following main topics - the use of drugs as a common etiological method of suicide and ways for pharmacists to find patients at high risk of suicide; suicide statistics, prevention and risk factors; learning through role-plays, empathy and compassion for suicidal patients.

In case of accidental poisoning, pharmacists can help prevent it by encouraging all users to use child-safe packaging and to keep all medicines out of reach. The information can be directed to those who take prescriptions for benzodiazepines, opioids, cardiovascular drugs and sedative-hypnotics, the most common drug toxicants. All citizens should be informed about the basics of first aid in case of poisoning by organizing information campaigns on the Internet, social networks, radio and television. Pharmacists can raise awareness by distributing anti-poisoning leaflets and directing users and patients to additional resources to learn about first aid for poisoning.

Economic evaluation of acute drug poisoning

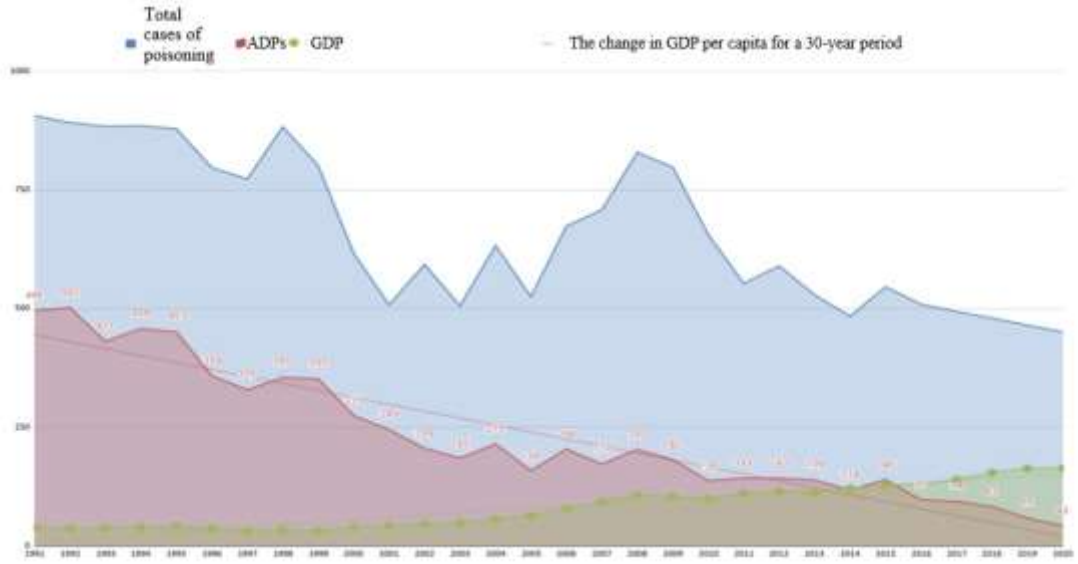

FIG. 21 Comparison of the change in GDP per capita for a 30-year period with ADPs as an aspect of a demographic survey of ADPs

With the improvement of the socio-economic situation of the population of Varna region in 2007. there is a downward trend in AMI and mortality. At the same time, there is an upward trend towards the combined use of different groups of drugs with / without alcohol, leading to the development of complications and prolongation of hospital stay. This may be due to the availability and increasing use of medicines among the population due to improved medical coverage and health insurance, as well as the fact that medicines are easy to obtain and use and due to the general ignorance about the harms expected from higher use. doses (Fig.21).

In this part, official public data on the clinical pathways from the NHIF are used. And the costs of treatment for the last years for diagnosis and treatment of poisonings and toxic effects of drugs

and household poisons - KP 107, agreed in the annex to the NDA between BMA and NHIF (Fig. 22) are summarized.

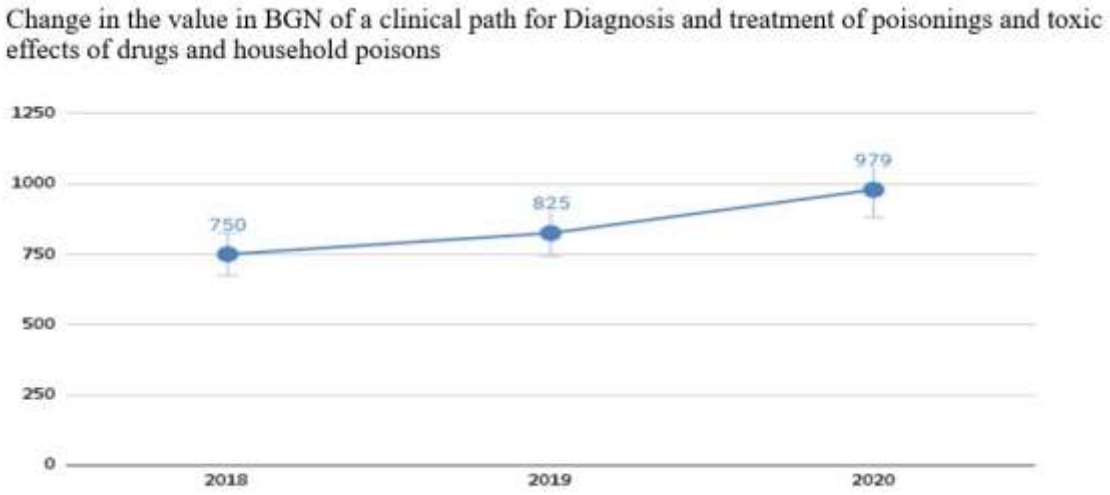

FIG. 22 Change in the value in BGN of a clinical path for Diagnosis and treatment of poisonings and toxic effects of drugs and household poisons

The graph shows the increase in the cost of hospital treatment of patients admitted to toxicology clinics. The economic impact of drug poisoning, as part of all acute intoxications, is significant for patients, healthcare facilities and society.

A full assessment of the costs of poisoning from a socio-economic point of view requires the inclusion of indirect costs, such as food, travel, accommodation and economic burden due to the loss of patients' ability to work. For this reason, the assessment is very difficult and limited. According to the authors, the overall impact of morbidity costs due to acute poisoning can exceed direct costs or be up to two to three times higher than expected direct costs.

The average number of days of hospital stay of patients with acute drug poisoning according to our data is 3 days. The maximum stay is 8-10 days, depending on the type of complications (heart block, nephropathy, pneumonia, etc.).

The value of direct costs is formed mainly by the drugs used for treatment; examinations and interventions, consumables, hospital stay. The components of indirect costs are determined by the loss of wages, food and transport.

The study found that the cost of managing acute drug poisoning decreased as the number of cases decreased, despite the increase in the value of the clinical pathway. Indirect costs are not included, as it is assumed that some of the costs, such as loss of salary, could continue after that.

Proper and competent education of patients regarding the need to adhere to the therapeutic course of treatment with prescribed drugs, duration of treatment, possible risks of concomitant use of

drugs from different pharmacological groups, dietary supplements and alcohol, could be a step to prevent of many of these events and costs to the public health system.

Discussion of the results

Data on the overall pattern of poisoning in each geographical region are important for preventing and reducing morbidity and mortality. The presented retrospective study of drug poisoning in the Varna region shows the number of patients admitted to the Clinic for treatment of acute poisoning and toxicoallergies and burns MMA Hospital - 6977. They represent 37.85% of all acute intoxications. Drug intoxications are more common in women - 71.4%. Men are 28.6%, the ratio of women: men is 2.50: 1 Intentional self-poisoning for suicide is 5914. Between 1991-2015, the highest relative share of benzodiazepine intoxications - 26.5%, followed by mixed OMO - 24.2%, while between 2016-2020 the percentage of combined drug intoxications increased - 36.76%, followed by 12.24% of combined intakes with alcohol and 10.56% of benzodiazepines. Fatal outcome was registered in 50. patients - 0.71%

The extremely high incidence of AMD at a young, working age suggests a milder course of these intoxications and a more favorable outcome, as serious concomitant diseases are much more common in elderly patients, which undoubtedly affect the course of poisoning and at the exit of it.

In recent years, according to the framework agreement with the NHIF, the minimum length of hospital stay for patients with acute drug intoxication is at least two days. Even if the condition of the patients allows a shorter hospital stay, they are not discharged from the medical establishments before the expiration of this term / so that the clinical path can be considered complete /. The mean length of hospital stay in orally poisoned patients in mild form was 3.0 days, while in those in severe form it was 6.74.

OMOs are most often the result of suicide attempts - 5914 / 89.6% /. Medications are the mainstay of suicide poisoning, and sedatives, antidepressants, and analgesics are most commonly used because of their availability.

The pattern of acute poisoning changes over time and varies from country to country and even between geographical area within the same country, which may also be due to differences in the socio-economic and cultural characteristics of the population. Various literature sources show variations in the age and sex distribution of poisoning cases. At European level, men in low- and middle-income countries account for the largest number, while in our study of acute drug poisoning, women predominate. A 2008 WHO report shows a regional distribution of global poisoning mortality, followed by Africa (8%), the Americas (7%), Europe (5%), the Eastern Mediterranean region (19%), and the Southeast Asian region (7%).) and in the West Pacific (7%) of total mortality.

The highest incidence of benzodiazepine or psychoactive drug poisoning has been reported in most studies. Other studies have reported the highest incidence of antidepressant and neuroleptic poisoning or antidepressant and analgesic poisoning. Data on intoxications in Poland indicate that pharmaceutical products are more often the cause of intentional (suicidal) and less often in case of accidental poisoning, and benzodiazepines are in the first place, followed by cardiovascular drugs.

For Romania, it was found that in 97.27% of attempts at acute drug poisoning, prescription drugs were used in 32.92% and 29.44% in drug combinations). In France, medicinal products are responsible for 40% of accidental poisonings in children and 80% of intentional poisonings in adults, with benzodiazepines being the main cause in 80% of cases.

Various studies in Turkey have identified other groups of drugs involved in poisoning - analgesics and antidepressants, due to their easy availability in the country's pharmacy network. Predisposing factors for acute deliberate poisoning include anxiety, depression, isolation, unemployment, marital disharmony, and failure.

Following the dynamics in the etiology of OMO, we find that some drug intoxications do not significantly change their frequency and relative share over the years, although the period under consideration is long - benzodiazepines, neuroleptics, anticonvulsants, cardiovascular, opiates, other drugs and drugs. Other drug intoxications increase their number slightly - antidepressants, NSAIDs. The frequency of mixed drug intoxications increases significantly, at the expense of reducing the frequency of single poisoning with benzodiazepines, sedatives and hypnotics. The amount and type of drugs used in combined intoxications are different, usually taking 2-9 drugs, OTC and dietary supplements for different therapeutic purposes. The absolute number of benzodiazepine intoxications decreased in 2015 compared to 1991 by 7.5 times.

Fatal outcome has been reported in 50 patients or 0.71% of drug intoxications, with the most common cause being mixed drug poisoning. The second most common cause of death is poisoning with drugs that affect the cardiovascular system - as verapamil poisoning caused death in 6 patients, and digitalis drugs in two. We have reported one death in paracetamol poisoning and as a result of long-term use of anabolic steroids. In the present study, drugs are the third most common cause of death after pesticide and alcohol poisoning. OMOs are responsible for 0.45% of all causes of death and reach a frequency of 3.58 / 100,000. A study in Germany reported a mortality rate of 0.7%, respectively, in patients diagnosed with acute drug poisoning. There are various reasons that can be presented to explain the variation in mortality in different countries. One of them is the healthcare system, training of medical staff on the identification and management of drug toxicity, criteria for admission to a toxicology clinic, infrastructure, socio-economic reasons, unregulated practices of purchasing prescription drugs freely in pharmacies.

Intoxications with calcium antagonists, beta-blockers, benzodiazepines, opiates, acetaminophen, tricyclic antidepressants and salicylates are associated with high risk and lethality.

From the presented analysis, a number of benefits can be derived from identifying high-risk patients to perform suicide attempts for drug poisoning. These are women up to 24 years of age. In order to prevent future events, it is of paramount importance to determine the motivation (s) of at-risk patients. To this end, preventive measures can be taken, including educational, regulatory and management approaches. Media and educational campaigns on the topic of acute poisoning are needed, as well as the active participation of general practitioners, nurses, pharmacists, teachers and pedagogical councils. There is a need to develop and disseminate messages aimed at raising awareness of the dangers of acute poisoning. Increase control over the implementation of the

ethical responsibilities of pharmacists, doctors and medical professionals in advising patients on the safe use and storage of over-the-counter or over-the-counter medicines.

Another possible role of the pharmacist in the control of poisoning is the establishment of a civic information and coordination unit at the municipal, national and international level. The proposed center can function as a main resource block for Bulgaria and the countries of the Black Sea region, between which there are the most intensive contacts and similarities in cultural and economic terms:

- Bulgaria
- Romania
- Ukraine
- Georgia
- Moldova

The Poison Coordination Center can be based on the extremely rich experience of Bulgarian physicians and pharmacists from the Varna region and provide information on the toxicity, risk and treatment of various types of substances. Such a center can also practically help to deal with poisonings, to systematically reduce the spread of drugs and other poisons by improving public awareness through the use of efficient, reliable and cost-effective methods, especially in modern environments such as the Internet and social networks, radio and television.

A Toxicological Vigilance Unit may be set up at the proposed center to identify and assess the toxic risks existing in the community and to assess the measures taken to reduce or eliminate them.

When a toxicological problem arises due to a change in the formula of a product, unclear label or instruction on the packaging, the emergence of new types of "designer drugs" or environmental pollution, pharmacists and doctors from the center warn the relevant health and administrative authorities, so that the necessary preventive and regulatory measures can be taken.

Pharmacists can participate in the development of an automated system for the analysis of acute poisoning, by summarizing and properly annotating data, the ultimate goal of which is to support the decision-making of clinical toxicologists in order to improve therapy and reduce hospital stays and costs in the system. of healthcare.

It is necessary to focus on four key areas:

- measuring the effectiveness of risk minimization measures

- measuring the effect of specific pharmacovigilance processes

- effective interaction with patients and healthcare professionals as key stakeholders

- development of methodologies for measuring the impact of acute poisonings on health

Knowledge and skills about the safety of drugs and their safe use in daily practice are important for all health professionals who are directly involved in pharmacotherapy, such as doctors,

pharmacists, dentists and nurses, to minimize harm to the patient. Competence in working with medicinal products in clinical practice is important not only for the safety of patients individually, but also for monitoring the safety of drugs at the population level / 66 /.

This creates preconditions for improving, deepening, directing the knowledge of medical staff at the university level on drug safety, which would modernize the culture in health care in terms of reporting ADRs and toxic phenomena and awareness of their reporting.

The WHO suggests that key aspects of the content of the core pharmacovigilance curriculum in medical universities should be:

- Understanding the importance of drug safety - historical examples and drug damage

- Prevention of ADRs and toxic effects when using medicinal products common risk factors, individual risk factors, treatment guidelines and safety information

- Recognition of ADRs and toxic reactions - Classification of ADRs and toxic reactions, risk factors, variables, epidemiology

- Management of ADRs and toxic reactions - assessment of severity, severity, selection of correct actions, communication between medical professionals, benefit-risk optimization, data recording

- Reporting of ADRs and toxicities - practical significance of the reporting of these phenomena, documentation of ADRs and toxic reactions, drug interactions, filling in forms and questionnaires.

Application structure for automated poisoning risk assessment

Once the classifiers are trained on a sufficient number of patient data, it is possible to create an automated mobile application. It is proposed that the data can be scanned with a mobile phone, processed in advance, sent via an encrypted connection to the cloud infrastructure of a coordination center, classified and transmitted for feedback to a pharmacist, doctor and patient. An opportunity can be created for additional training of the system with the help of new data provided by a doctor, pharmacist or patient.

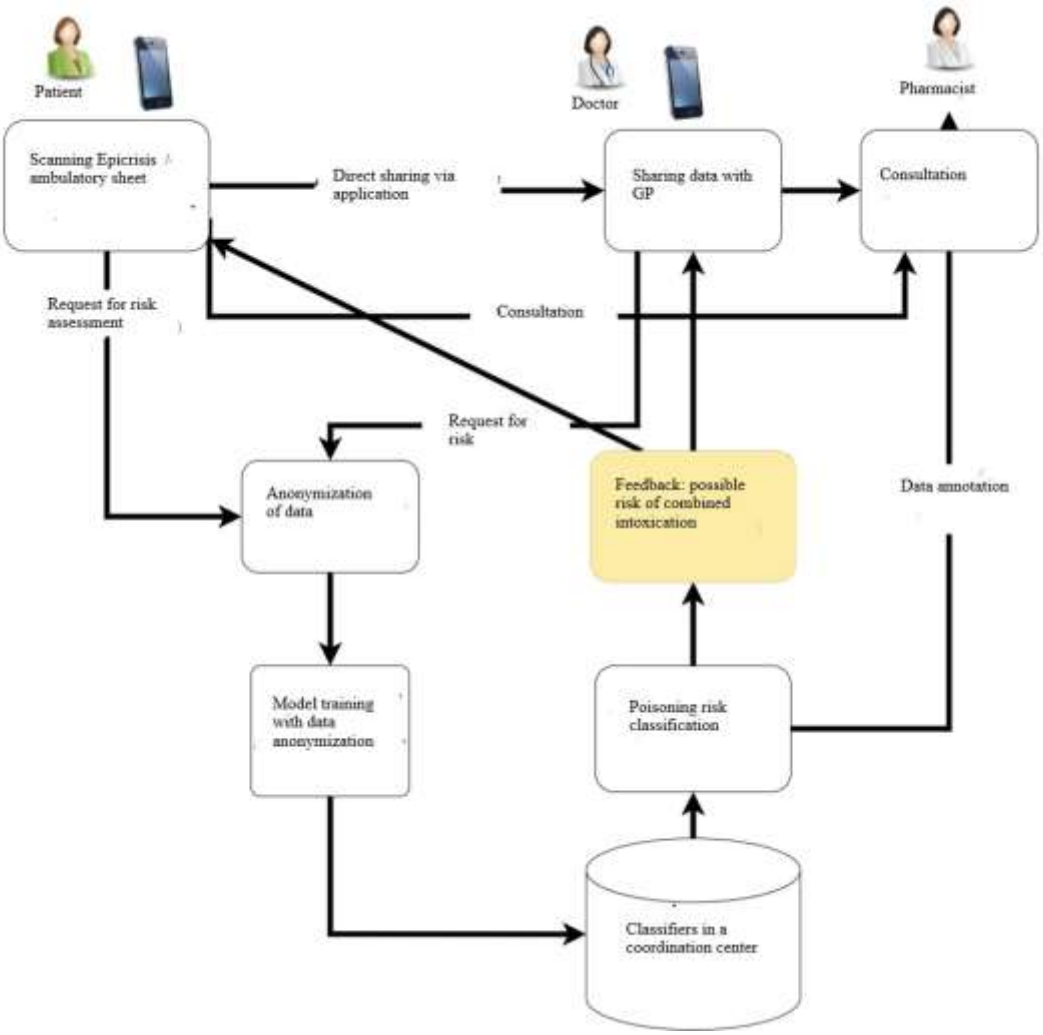

FIG. 23 Diagram of the process of operation of a mobile application for automated risk assessment of drug poisoning and coordination center

It is necessary for the patient to scan part of the epicrisis / outpatient list with prescribed therapy for home treatment and / or packaging of medicinal products, food supplements, currently used medical devices and data on possible alcohol consumption. This data is shared with the GP or sent to the focal point with a risk assessment request. Even on the mobile device, the data is subjected to an anonymization process. The process of classifying the risk and providing feedback to the patient follows. The information obtained can be discussed with your doctor or pharmacist.

A doctor receives information from a patient through an application, with a scanned part of the epicrisis / outpatient list with prescribed therapy for home treatment by a specialist, used nutritional supplements. Together with the part of the patient's file containing medicinal products for chronic use, it can be sent to the coordination center for assessment of the risk of the newly combined drug therapy and the risk of intoxication.

The pharmacist has the role of consultant to the patient or physician, and has the ability to annotate or correct a set of new or existing data as needed.

The presented statistical methods and approach for analysis of natural language documents with epicrisis of patients can be used to create a model / s of AMI, specific to a particular region, taking into account their features - qualitative and quantitative.

Conclusions

From the research and analyzes performed, in view of the research tasks, the following main conclusions can be formulated:

1. The most common etiological causes of acute drug poisoning are benzodiazepines, followed by combined drug intoxications, cardiovascular drugs, sedative-hypnotics and neuroleptics.

2. Independent intoxications with benzodiazepines, neuroleptics, anticonvulsants, cardiovascular, opiates do not significantly change their frequency and relative share during the period under review. The incidence of mixed drug intoxications is significantly increased. The amount and type of drugs used in combined intoxications are different, usually taking 2-9 drugs, OTC and dietary supplements for different therapeutic purposes

3. The demographic characteristics of patients in terms of age and sex remain relatively constant over a 30-year period. Acute drug poisonings predominate in females - 71.4%, while in men they are registered - 28.6%. The largest number of admitted patients with acute poisoning was in the age groups: up to 24 years of age (46.37%) and 25-44 years (33.73%).

4. For the last 5 years of the study, attempts at intentional self-poisoning accounted for 65.5% of all patients with acute drug intoxications admitted to the toxicology clinic, which revealed suicide as a significant health and social problem for which preventive measures needed to be taken. .

5. Fatal outcome was found in 50 of the cases or 0.71%, which shows the ability for good management and treatment of poisoning by medical professionals from MHAT to MMA-Varna.

6. There is a decreasing trend of AMI towards the increase of the gross domestic product per capita for the indicated period. The cost of managing acute drug poisoning decreases as the number of cases decreases, despite the increase in the value of the clinical pathway.

7. It is necessary to increase the awareness and knowledge of health professionals and pharmacy students about accidental or intentional drug poisoning. There is also a need for discussion between universities, municipal and state institutions, patient organizations and other stakeholders on the health and social risks of drug intoxication.

Summary

The analysis conducted in the framework of the present dissertation points out the acute drug poisonings as a serious health and social problem for the society. The Clinic for Treatment of Acute Poisoning and Toxic Allergies and Burns of the Military Medical Academy - Varna received 6977 for the period from 1991-2020, of which 5914 / 89.6% / were the result of suicide attempts. From a demographic point of view, this type of intoxication predominates in women - 71.4%. The most common etiological causes for the period 1991-2015 are benzodiazepines - 26.5%, followed by mixed OMO - 24.2%, while between 2016-2020 there is an increase in the percentage of combined drug intoxications - 36.76%, followed by 12.24% of the combined intake with alcohol and 10.56% of benzodiazepines. Fatal outcome was registered in 50 patients - 0.71%.

Contribution

Contributions of confirmatory, scientifically applied and original nature:

● For the first time, a description of acute drug poisoning in the Varna region for a period of 30 years (1991-2020) was made and a statistical analysis was prepared in terms of demographic and etiological indicators, on the basis of which measures can be taken to improve and optimize of medical care for the population, as well as the development of effective preventive measures, as well as those for rehabilitation, aimed at reducing the impact of toxic factors as a cause of preventable morbidity and mortality.

● The typical toxicodromes in drug poisoning and treatment methods are summarized. A specific emergency form and selection of therapeutically effective dosage forms can be proposed and developed in any modern treatment center, as well as advanced training of pharmacists in order to assess and prevent cases of poisoning or refer intentional cases of poisoning to a psychologist or psychiatrist, specific educational programs.

● For the first time, an approach has been developed and a platform for anonymization of clinical data of patients compliant with the EU regulation on personal data protection (GDPR) has been proposed and an approach for analysis and prerequisites for implementation of a software application for visualization of clinical data has been proposed. data in mobile devices.

● For the first time, an approach for training a model and classifiers for patient documents containing text in natural language has been proposed, which has the ability to assess the possible risk of combined drug intoxication and an algorithm for building a mobile application with trained models has been proposed. classifiers to a poisoning coordination center of international and national importance.

● For the first time, the roles of pharmacists as consultants in poisoning, data annotation and assessment of toxicity risk models are presented, and additional training of pharmacists and pharmacy students is needed on prevention and prevention of suicide trials with medicinal products.

List of publications on the topic

- Stanislava Georgieva, Petko Marinov “Nutritional toxicology - an overview”, PROCEEDINGS Vol. 58, book 10.2. - 2019 Biotechnologies and Food Technologies

- Stanislava Georgieva, Nadya Agova “Risk of liver injury during use of dietary supplements” Management and education vol.16 (6) 2020

- Stanislava Georgieva "Toxicological characteristics of chloroquine and hydroxychloroquine", "Notices of the Union of Scientists - Ruse" Series 4 "Medicine and Ecology" ISSN 1311-1078P

- Stanislava Georgieva, Petko Marinov “Toxicologic overview of garden plants”, Scientific and practical conference - VI Varna Pharmaceutical Business Forum - Varna 2019 - poster

- Stanislava Georgieva, Strahil Sokolov, Petko Marinov “New potential toxicants -“ fake ”medicines”, Scientific and practical conference - V Varna Pharmaceutical Business Forum - Varna 2018 - poster

- Stanislava Georgieva, Petko Marinov, Strahil Sokolov, “Overview of Recent Cases of Drug Intoxication in The Black Sea Region”, 12th Conference of Macedonian Society of Toxicology with International participation, March 19-21.2019 - poster