

Statement

By Prof. Zlatka Dimitrova Dimitrova, DSci, Head of UNAL in Social Pharmacy, Department of Physical Chemistry, Faculty of Chemistry and Pharmacy at Sofia University "St. Kl. Ohridski" - Sofia, appointed a member of the Scientific Jury by order №P-109-337 / 09.08.2021 of Prof. Dr. Albena Kerekovska, MD-Director of the Directorate "Educational Activity", for Rector of MU "Prof. Dr. Paraskev Stoyanov" Varna, according to order №P-100-431 / 13.07.2021

Subject: procedure for defense of a dissertation on the topic: "CHARACTERISTICS OF ACUTE MEDICINAL POISONING IN THE VARNA DISTRICT FOR A 30-YEAR PERIOD" for the acquisition of ESD "Doctor" of mag. farm. Stanislava Angelova Georgieva, PhD student in full-time education in the field of higher education 7. Health and Sports, Professional field 7.3 Pharmacy, in the doctoral program "Toxicology" with supervisors: Prof. Dr. Petko Penkov Marinov, MD and Prof. Antoaneta Zdravkova Tsvetkova, Ph.D.

This statement has been prepared in accordance with the requirements of ZDASRB, RAZDASRB and the Regulations for the development of the academic staff at MU "Prof. Dr. P. Stoyanov" - Varna in force since 15.09.2020 (protocol №8 / 15.09.2020), Chapter II. Acquisition of scientific degrees, Section IV. Conditions and procedure for acquiring ONS "Doctor".

Details of the procedure. With Order №P-109-432 / 16.07.2018 mag. farm. Stanislava Angelova Georgieva is enrolled as a PhD student in full-time education in the field of higher education 7. Health and Sports, Professional field 7.3 Pharmacy, in the doctoral program "Toxicology" in the Department of Pharmacology, Toxicology and Pharmacotherapy at the Faculty of Pharmacy, MU-Varna. A protocol from 05.09.2019 was presented for successfully passed the exam for covering the doctoral minimum in the specialty of toxicology by the PhD student before a commission appointed by order of the Rector of MU-Varna, as well as Order № P-109-314 / 21.07.2021 for expulsion of the doctoral student with the right to defend the dissertation after its discussion by the department council and a decision on its readiness for referral for public defense. The PhD student's file folder contains all the required documents

Biographical data and career development of the candidate: mag. farm. Stanislava Angelova Georgieva graduated in pharmacy and obtained a master's degree in pharmacy in December 2015 in FPh at MU-Varna. She worked in pharmacies in the city as an assistant pharmacist and master pharmacist and since April 2017 she has been the head of the faculty pharmacy "Medunipharm". Along with performing her current tasks in the pharmacy, she participates in the training of students and trainee pharmacists in the pharmacy entrusted to her.

Relevance and significance of the dissertation. Knowledge of poisons began to accumulate at the dawn of human civilization. The first Philip Oreolus Theophrastus Bombastus von Hohenheim (1493–1541), called Paracelsus, was the scientist who initiated the concept of "toxicity" with his immortal sentence "Dosis sola facit venenum". According to him: "All substances are poisons, there is no one that is not poison. The right dose distinguishes poison from medicine, ie there are no harmless chemicals, only harmless ways to use them. According to the WHO, approximately 200,000 people die each year from unintentional intoxications and one million die from suicide. The pre-hospital mortality in acute intoxications is usually about

80%, while the hospital mortality does not exceed 2-3%. Given the significant prevalence of toxicological nosological units (400 per 100,000 population), there is a high mortality rate from poisoning, which significantly exceeds the incidence of deaths from infectious and other common diseases. According to these indicators, acute intoxications in the United States and Europe are in one of the top three places in all rankings. Acute intoxications are among the most common causes of emergency hospitalization worldwide, and still in a high percentage end in death. It is no coincidence that Prof. Monov, founder of modern Bulgarian clinical toxicology, expressed the opinion that modern man lives in conditions of "toxicological aggression". That is why AMI is among the main socially significant problems of modern society. In the toxicology clinic of MHATEC "N. I. Pirogov" an analysis of the poisonings and self-poisonings performed with benzodiazepines, which are the leading drugs in the drug list of intoxications and in the research of the PhD student. It was found that the leaves of toxicological pathology lack drugs such as diazepam, nitrazepam, medazepam, chlordiazepoxide, but new ones appear or newer ones increase - bromazepam, clonazepam, cinolazepam. This trend is even more pronounced with antidepressants. Poisonings with amitriptyline and maprotiline are very rare, at the expense of citalopram, paroxetine, flupentixol, melitrasen and others. The hypnotic drug zopiclone has completely displaced the combination of amobarbital, glutethimide, promethazine. Poisoning with psychoactive substances is growing, and the type of noxia is changing. Exogenous intoxications with heroin have increased, there are those with amphetamines, cannabis, cocaine, methadone, ecstasy. The analysis made in MHATEC "N. I. Pirogov" concludes with the conclusion about a change in the spectrum of noxa in exogenous intoxications in our country. In a study at the Clinic "Emergency Toxicology" of MHAT-Sofia of the Military Medical Academy are presented MP, which are the most common causes of drug intoxication in our country. The majority of deaths from poisoning in the United States have been drug-related. The U.S. Food and Drug Administration (FDA) has approved a new dosage form (autoinjector) to save the lives of thousands of people from opiate overdoses by using of antidote - Naloxone. The WHO recommendation is to reduce the number of opioid-related deaths and increases public access to naloxone. According to the WHO, every adult is able to learn to recognize "opiate overdose" and, if necessary, to apply the antidote in time to save lives. Placed in a new dosage form - a pocket-sized autoinjector, the product with the patent name Naloxone, changes in a favorable direction the outcome of one of the most severe intoxications - an overdose of narcotic drugs. Included, the device gives verbal instructions to the user and enough time to transport to the hospital. If the signs and symptoms have nothing to do with opioid intoxication, the injection is ineffective. The pharmaco-therapeutic guide "Antidotes in the golden hour of emergency toxicology" presents the current trend in the treatment of acute intoxications, namely the multidisciplinary approach. In recent years, the efforts of multidisciplinary teams have focused on finding not only new drugs and therapeutic combinations to deal with acute and chronic intoxications, but also on developing a comprehensive organizational algorithm of behavior. Cases of suicide by poisoning are particularly common in the Scandinavian countries and Britain. Therefore, this dissertation, despite the fact that it is a regional study and covers patients over 13 years /, ie. there is no data on acute poisoning in children up to 12 years / is dedicated to a significant problem for public health and is very relevant. It is in a volume of 160 pages, distributed as follows: 1 page - introduction, 39 pages - literature review, 9 pages -

research methodology, 81 pages. -results and their discussion, conclusions. The bibliography includes 260 titles, arranged in the order of their citation, of which only 6 are in Cyrillic and the rest in Latin.

General characteristics of the candidate's research and applied research activity.

Due to the imperfection of the reporting of acute poisonings, to date in our country there is no objective picture of the situation, both at central and regional level. The Northeastern region has a population of 922,230 people, and MHAT-Varna - Military Medical Academy is the only medical institution in Northeastern Bulgaria with a specialized clinic for the treatment of acute poisoning and toxic allergies. The analysis conducted within the framework of this dissertation for a period of 30 years points out the acute drug poisonings as a serious health and social problem for the region. The Clinic for treatment of acute poisonings and toxic allergies and burns of the Military Medical Academy - Varna received 6977 for the period from 1991-2020, of which 5914 / 89.6% / are 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 AMI - 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%. References are made to similar studies by authors in other countries who support or explain the results of this study. With the improvement of the socio-economic situation of the population of Varna region after 2007. there is a declining trend in AMI and mortality from them. 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.

In the dissertation of mag. farm. Stanislava Angelova Georgieva there is also an educational element: the main sections in the theoretical part of the dissertation are competently and fascinatingly described: Historical review of poisoning research, Definitions, Types of poisoning, Classification of poisoning and toxic agents, Epidemiology of acute drug poisoning, Acute drug poisoning, Assessment of the severity of poisoning (OTO), General principles in the treatment of acute poisoning and Strategies for prevention and control of acute drug poisoning. European poisoning control organizations and centers in their annual reports and each section is supported by relevant references.

The dissertation uses a rich and varied, well-presented modern tools, adequate to perform the tasks. The PhD student used modern approaches in the field of artificial intelligence for statistical processing and data analysis. Attention is paid to modern methods such as NLP (Natural Language Processing - NLP) -processing of natural-language information from the discharge summary of patients in the Python programming environment with selected library scikit-learn for the development of a computer application for the benefit of the patient, doctor and pharmacist and to create a mathematical model for assessing the risk of drug intoxication depending on the medicinal products and food supplements taken by the patient in combination with or without ethanol. Both applications would find practical implementation in the possible future construction of a coordination center for poisoning.

The study is a longitudinal comprehensive retrospective regional study of an important problem for medical science and practice. The conclusions in the dissertation work derive from the conducted analyzes and from the obtained results and are clearly formulated.

Main scientific and applied scientific contributions. The main scientific and scientific-applied contributions in the dissertation are new scientific facts in the field of acute exogenous drug intoxications and possibilities for their prevention. They are the result of those conducted by Mag. farm. Stanislava Angelova Georgieva research and can be summarized as follows:

ORIGINAL CONTRIBUTIONS:

- Huge factual material on poisonings and self-poisonings for persons over 13 years of age in Varna region for a 30-year period (1991-2020) was analyzed and the significance of sex, age and dynamics by years of etiological indicators was assessed, based on which to take measures to reduce the impact of toxic factors as a cause of preventable morbidity and mortality.

SCIENTIFIC-APPLIED CONTRIBUTIONS:

- A platform for anonymization of clinical data of patients, compliant with the EU regulation on personal data protection (GDPR) and an approach for implementation of a software application for visualization of clinical data on mobile devices is proposed.

- A program application program has been proposed to assess the risk of combined drug intoxication and an algorithm for building a mobile application to a poisoning coordination center of national and / or international importance.

Reflection of the candidate's scientific publications in the literature

On the topic of the dissertation are presented 4 published scientific articles and 3 participations with posters at scientific forums at home and abroad.

Critical remarks and recommendations to the candidate

There are small inaccuracies in the dissertation, missing words of some figures and stylistic and spelling mistakes that do not reduce its value. Thus e.g. I would recommend to change the numbering of Fig. 13-24 in Fig. 10.1-10.10, as these are modifications of the main Fig. 10 in view of the independent discussion of the results of the study on the separate subgroups by etiological feature of AMI.

The proposal for the establishment of a Poison Coordination Center for the countries mentioned in the literature review should be made in my opinion at the end of the dissertation in the section Conclusions and recommendations and this need should be justified by the results of the study.

It would be interesting in the future to pay attention to and assess the financial burden of AMI in the Varna region for the health care system and society in the region through an appropriate pharmaco-economic analysis/ research task 1.6 /

Conclusion. The dissertation of mag. pharmacist Stanislava Angelova Georgieva contains new scientific facts of special relevance and significance for the field of drug toxicology. The results of the research in the dissertation and their interpretation are at a high scientific level, they are published in the specialized literature and are reported at scientific forums on toxicology at home and abroad. The scientific work fulfills all the requirements of ZDASRB and of the Regulations for its application / RAZDASRB / and of the Regulations for development of the academic staff in MU "Prof. Dr. P. Stoyanov" - Varna for acquiring ESD "Doctor". I give a positive assessment of this dissertation and will fully support the award of the ESD "Doctor" to the mag. pharmacist Stanislava Angelova Georgieva in the PhD program "Toxicology" by voting "For".

October 10, 2021, Sofia


Prof. Zl. D. Dimitrova, DSci.