

Immunological Criteria of Autoaggression of Bronchial Asthma: Markers for Prediction of the Course and Selection of Adequate Pharmacotherapy

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Abstract. About 10% of the population of highly developed European countries suffer from bronchial asthma. Monitoring for the period 2014-2021 regarding the number of patients with bronchial asthma in the Lviv region showed an increase in dynamics. The prevalence of bronchial asthma among the population is much higher, because patients do not always consult an allergist, but are treated by other specialists. This is a serious problem today, as blood pressure reduces the quality of life and work capacity of patients. Against the background of the increasing incidence of bronchial asthma, the frequency

of the severe course of this disease is also increasing, which takes on the character of autoaggression and requires the use of increasing doses of glucocorticoids during treatment, up to daily replacement therapy. Accordingly, it is important to establish the immunological criteria of autoaggression in blood pressure markers for predicting the severity of the course and choosing an adequate drug treatment.

Keywords: bronchial asthma, immunological status, hormone dependence, autoaggression, prognostic markers, pharmacotherapy, drugs.

Introduction. According to the WHO estimates, in 2019, 262 million people worldwide suffered from bronchial asthma, which caused 455,000 deaths [1]. In the highly developed countries of Europe, about 10% of the population suffers from bronchial asthma [2]. Among the EU countries, Finland is in the lead – 9% of asthma patients; Germany and France – 8% each; Romania and Bulgaria – 2% [3]. In Ukraine, according to the Center for Medical Statistics of the Ministry of Health, in 2017, 212,883 patients with asthma were registered, of which 37,427 were children [4].

Bronchial asthma is a serious problem today. It reduces the quality and length of life, affects the working capacity of patients. Against the background of the increase in the incidence of bronchial asthma, the frequency of the severe course of this disease is also increasing. Acquires the character of autoaggression. It requires the use of increasing doses of glucocorticosteroids in pharmacotherapy.

In previous studies Nevzhoda A.A. and Nevzhoda O.A. during 2015-2021 [5-10], according to foreign (Salvi S.S., Kim D.S., Zhou Y., etc.) [11-23] and domestic (Zerbino D., Ryabukha O., etc.) [24-26] scientists established a connection between the autoaggressive course of lung diseases and changes in the immune status in terms of the quantitative and qualitative composition of circulating immune complexes, T-lymphocytes, 0-lymphocytes, and D-lymphocytes. This requires further multidisciplinary research in the chain of legal relations "doctor-patient-pharmacist" during the access of privileged categories of citizens to vital drugs, the circulation of which is carried out on the principles of medical and pharmaceutical law (Haiduchok I.G., Shapovalova V.O., Ishcheykin K.E., Chopyak V.V., Gudzenko A.O., etc.) [27-33]. Therefore, the study of the indicators of immunity in the autoaggressive course of the infectious-allergic form of bronchial asthma has been continued.

The purpose of the study was to establish the immunological criteria of autoaggression of bronchial asthma as markers for predicting the severity of the course and choosing adequate pharmacotherapy with the use of vital drugs.

Material and methods. To achieve the goal, the author conducted a search and studied available domestic and foreign scientific sources of literature related to the latest results of

immunological criteria of autoaggression of bronchial asthma. The methods used were: documentary, statistical, bibliographic, semantic, descriptive modeling, and system approach.

The study is a fragment of the research work of Lviv Medical University LLC on the topic "Improving the system of drug circulation during pharmacotherapy on the basis of evidence-based and clinical pharmacy, organization, technology, biopharmacy and pharmaceutical law" (state registration number 0120U105348, implementation period 2021-2026).

Results and discussion. An important point is the study of official data on the number of patients with bronchial asthma which are registered in health care institutions. Thus, in 2014 in the Lviv region among the adult population it was recorded [34]:

- 9,200 patients with bronchial asthma;
- 2500 cases of pollinosis;
- 5900 – allergic rhinitis.

Among children:

- 1,822 cases of bronchial asthma (4.5 per 1,000 children);
- allergic rhinitis – 4,371 (10.8 per 1,000 children);
- atopic dermatitis – 7325 (18.3 per 1000 children).

Experts note that the prevalence of bronchial asthma is increasing in the Lviv region. At the same time, the prevalence of asthma among the population is much higher, because patients do not always consult an allergist, but are treated by other specialists.

Further studies showed that from the beginning of 2021, about 12,260 patients with allergic diseases were recorded in the Lviv region: allergic rhinitis, bronchial asthma, urticaria, allergic conjunctivitis [35, 36]. The share of allergic rhinitis among detected allergic pathologies is 42%. In Lviv, a regional center of clinical immunology and allergology, which uses new methods of allergen-specific immunotherapy, has been operating for more than 20 years on the basis of the Lviv Regional Clinical Diagnostic Center. Allergology and immunology experts of the Lviv Regional State Health Department note that in the first half of 2021, there were no deaths due to bronchial asthma or drug allergies.

As of December 11, 2022, there are 9,329 citizens registered with bronchial asthma in the Lviv Region [36]:

- 4787697 patients older than 18 years;
- 478 – teenagers;
- 1154 – children up to 14 years old.

Need to note that among the factors that provoke or worsen the symptoms of bronchial asthma are [37-53]:

- ✓ viral infections (COVID-19, etc.);
- ✓ household (house dust mites, plant pollen, cockroaches) and/or professional allergens;
- ✓ smoking, alcoholism, drug addiction, use of medicines not prescribed by a doctor;
- ✓ physical exercises, environmental safety;
- ✓ psychoneurological health disorders (according to ICD-10, ICD-11);
- ✓ drugs (acetylsalicylic acid, nonsteroidal anti-inflammatory drugs).

Subsequently, in the period from 2015 to 2022, the 2nd group of patients with an infectious-allergic form of bronchial asthma were examined. Each group consisted of 100 patients aged 18-65, 50 men and 50 women, respectively. The control group consisted of 50 clinically healthy volunteers of similar age and sex. An immunogram was performed on all patients upon initial admission to the pulmonology department of the hospital. The criterion for the presence of an infectious-allergic form of asthma with a broncho-obstructive form of respiratory failure is spirometry:

- with $FEV_{1\text{ sek}}/FVC < 80\%$ of predicted, which is a global indicator in pulmonology;
- values of peak expiratory volume velocity (PEV) and forced expiratory volume of the first second (FEV_1) $< 80\%$ of the appropriate values;
- pronounced reversibility of bronchial obstruction – an increase in the level of PEV and $FEV_1 > 12\%$ (or ≥ 200 ml) according to the results of a pharmacological test with a short-acting β_2 -agonist;

- daily variability of PEV and $FEV_1 > 20\%$.

As screening tests for determining changes in the immunological state in this pathology, we have proposed studies of the content of examined T-, O- and D-lymphocytes, large and small circulating immune complexes (CIC) in the blood serum. Immune complexes consist of antigens, antibodies, and related components of complement C3, C4, C1q. Normally, immune complexes formed in the bloodstream are phagocytosed and destroyed. When their size increases (with an excess of antigens and the presence in their structure of IgM, a component of complement C1q), the complexes can be deposited in the perivascular space and cortical layer of the kidneys, causing complement activation and inflammatory processes.

Determination of the content of immune complexes in blood serum is important in the diagnosis of acute inflammatory processes and allergic reactions, in which the level of CIC increases, as well as in the evaluation of the effectiveness of the pharmacotherapy. In autoimmune diseases, tissue-reacting autoantibodies appear, which have a cytotoxic effect, but immune complexes provide an incomparably greater damaging effect. The obtained data highlighted in the Table 1.

Table 1. Indicators of the immunogram in the severity of the course of the infectious-allergic form of bronchial asthma.

Indicators of immunity	Control group Clinically healthy individuals	Patients with an infectious-allergic form of bronchial asthma with an autoaggressive course	Patients with an infectious-allergic form of bronchial asthma without autoaggression
O-lymphocytes	31,6±0,6	45,4±1,1 P<0,001	32,5±1,5 P<0,001
D-lymphocytes	1,4±0,8	4,2±0,6 P<0,001	1,5±0,6 P<0,001
CIC-small	37,7±0,3	64,1±1,4 P<0,001	41,4±1,8 P<0,001
CIC-large	59,1±0,15	37,3±0,75 P<0,001	62,3±1,5 P<0,001
Number of examined N=250	50	100	100

The dynamics of the study of the above-mentioned (obtained) indicators among patients of the examined groups indisputably proved the growth of the hypoimmune and autoaggressive component in patients with an infectious-allergic form of bronchial asthma.

Subsequently, the specified groups of patients were observed for 3 years. Information was obtained about the severity of the autoaggressive component in the infectious-allergic form of bronchial asthma and its stability.

Established that clinically the studied number of autoaggressive diseases was characterized (Fig. 1):

- ✓ damage to 2 or more organ systems is observed in the clinic of the disease;
- ✓ constant subfibrillation or hyperthermia is observed in the clinic of the disease;
- ✓ progressive diseases are often fatal and have severe complications;
- ✓ always a positive clinical effect when using glucocorticosteroids.

The specified features were detected during the examination of patients with an autoaggressive course of the infectious-allergic form of bronchial asthma, which proves the transition of the disease to an autoaggressive state. Clinically, in infectious-allergic form of bronchial asthma, excess weight, pregnancy, use of antibacterial drugs with bactericidal effect were observed as an aggravating factor. A positive factor was the use of antibiotics with bacteriostatic

properties. Rapidly increased pulmonary hypertension in the small blood circulation with left ventricular heart failure.

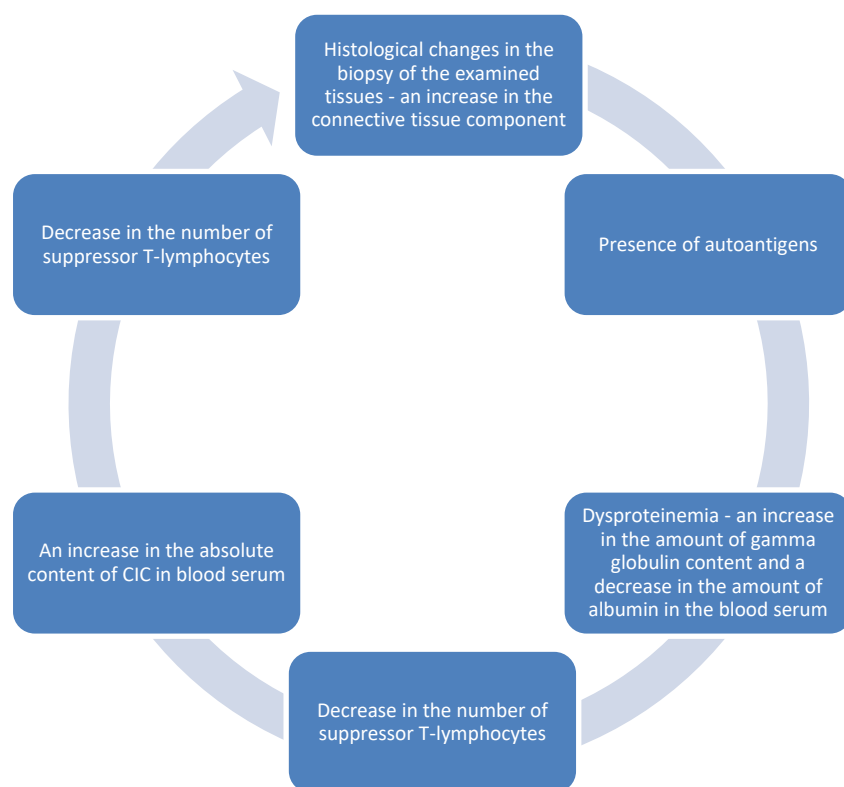


Fig. 1. Immunological criteria of autoaggressiveness of autoimmune diseases.

Thus, the establishment of immunological criteria of autoaggression of bronchial asthma as markers for predicting the severity of the course and the selection of adequate pharmacotherapy with the use of vital drugs has been worked out.

Conclusions. Monitoring for the period 2014-2021 regarding the number of asthma patients in the Lviv region shows the dynamics of increase. The prevalence of bronchial asthma among the population is much higher, because patients do not always consult an allergist, but are treated by other specialists. The dynamics of the study of the above-mentioned indicators among patients of the examined groups indisputably proved the growth of the hypoimmune and autoaggressive component in patients with an infectious-allergic form of bronchial asthma. Immunological indicators of autoaggression are the basis for the use of glucocorticosteroids in pharmacotherapy (usually in a dose of at least 10 mg/day in terms of prednisolone). The presence of immunological indicators of autoaggression predicts the possibility of transformation of the infectious-allergic form of bronchial asthma into systemic autoimmune diseases, clinical over-lap syndrome.

Conflict of interests. The authors confirm that they are the authors of this work and have approved it for publication. The authors also certify that the obtained clinical data and research were conducted in compliance with the requirements of moral and ethical principles based on medical and pharmaceutical law, and in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

Ethical approval. Ethical clearance was obtained from the administration of Lviv Medical University LLC. A permission statement for conducting the experiments was received from the administration of Lviv Medical University LLC. Before any data collection, the main purpose of the study was clearly explained to each department (concerned personnel).

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References.

1. Asthma. *WHO*. 11.05.2022. URL: <https://www.who.int/news-room/fact-sheets/detail/asthma>.
2. Kavanagh J., Jackson D.J., Kent B.D. Over- and under-diagnosis in asthma. *Breathe*. 2019. Vol. 15: No. 1. P. 20-27. URL: <https://breathe.ersjournals.com/content/15/1/e20>
3. Finland: EU country with highest share of asthmatics. *Eurostat*. 24.09.2021. URL: <https://ec.europa.eu/eurostat/web/products-eurostat-news/-/edn-20210924-1>.
4. Svezhentseva I. Day of patients with bronchial asthma. What everyone should know. *Suspilne.Media*. 11.12.2021. URL: <https://suspilne.media/188425-den-hvorih-na-bronhialnu-astmu-so-varto-znati-koznomu/>.
5. Kushinska I., Nevzhoda A. If the temperature suddenly drops from high to below 36, then, as a rule, on the second or third day - pneumonia. *WZ.Lviv.Ua*. 25.03.2020. URL: <https://wz.lviv.ua/life/409096-anatolii-nevzhoda-yakshcho-temperatura-z-pidvyshchenoi-rizko-padaie-do-nyzhche-36-to-iaak-pravylo-na-druhyi-tretii-den-pnevmonii>.
6. Half a glass three times a day: Lviv doctors received a patent for the treatment of coronavirus. *Vgorode*. 09.11.2020. URL: <https://lviv.vgorode.ua/news/sobytyia/a1139216-po-piv-charki-trichi-na-den-lvivski-likari-otrimali-patent-na-likuvannja-koronavirusu>.
7. In Lviv, they patented their method of treating coronavirus pneumonia. *4studio*. 31.01.2021. URL: <https://4studio.com.ua/novyny/u-lvovi-zapatentuvaly-svij-metod-likuvannja-koronavirusnoyi-pnevmoniyi-video/>.
8. Lviv doctors received a patent for the treatment of coronavirus with alcohol. *Ukrainian reporter*. 08.02.2021. URL: <https://ukrreporter.com.ua/suspilstvo/lvivski-likari-otrymaly-patent-na-likuvannja-koronavirusu-spytrom.html>.
9. Lviv medical brothers patented a new method of treating COVID-19 with alcohol. *LMN*. 01.02.2021. URL: <https://www.lmn.in.ua/lvivski-braty-medyky-zapatentuvaly-novyj-metod-likuvannia-covid-19-spytrom/>.
10. Kushinska I., Nevzhoda A. If the temperature is high and suddenly drops below 36 degrees, this indicates that there may be pneumonia. *Interview from Ukraine*. 06.08.2020. URL: <https://rozmova.wordpress.com/2020/08/13/anatolij-nevzhoda/>.
11. Salvi S.S., Barnes P.J. Chronic obstructive pulmonary disease in non-smokers. *The Lancet*. 2009. Vol. 374. Iss. 9691. P. 733-743. DOI: [https://doi.org/10.1016/s0140-6736\(09\)61303-9](https://doi.org/10.1016/s0140-6736(09)61303-9).
12. Kim D.S., Kim Y.S., Jung K.-S. et al. Prevalence of chronic obstructive pulmonary disease in Korea: a population-based spirometry survey. *Am. J. Respir. Crit. Care. Med*. 2005. No. 172(7). P. 842-847. DOI: <https://doi.org/10.1164/rccm.200502-259OC>.
13. Zhou Y, Wang C, Yao W. et al. COPD in Chinese nonsmokers. *Eur Respir J*. 2009. No. 33(3). P. 509–518. DOI: <https://doi.org/10.1183/09031936.00084408>.
14. Ehrlich R.I., White N., Norman R. et al. Predictors of chronic bronchitis in South African adults. *Int. J. Tuberc. Lung. Dis*. 2004. No. 8(3). P. 369-376.
15. Forbes L., Kapetanakis V, Rudnicka A. et al. Chronic exposure to outdoor air pollution and lung function in adults. *Thorax*. 2009. No. 64(8). P. 657-663.
16. Hopkinson N.S., Polkey M.I. Chronic obstructive pulmonary disease in non-smokers. *The Lancet*. 2015. No. 374 (9706). P. 1964.
17. Hopkinson N.S., Molyneux A., Pink J. et al. Chronic obstructive pulmonary disease: diagnosis and management: summary of updated NICE guidance. *BMJ*. 2019. No. 366. P. 4486
18. Doust E., Ayres J., Devereux G. et al. Is pesticide exposure a cause of obstructive airways disease? *Eur. Respir. Rev*. 2014. No. 23(132). P. 180-192.
19. Arroyave M.E. Pulmonary obstructive disease in a population using paraquat in Colombia. *World Environmental Library*. 1993. P. 1-7.
20. Lamprecht B., Schirnhofner L., Kaiser B. et al. Farming and the prevalence of non-reversible airways obstruction – results from a population-based study. *Am. J. Ind. Med*. 2007. No. 50(6). P. 421-426.

21. De Jong K., Boezen H.M., Kromhout H. et al. Original contribution association of occupational pesticide exposure with accelerated longitudinal decline in lung function. *Am. J. Epidemiol.* 2014. No. 179 (11). P. 1323-1330.
22. Kemp J.P. Recent advances in the management of asthma using leukotriene modifiers. *Am. J. Respir. Med.* 2003. No 2(2). P. 139-56. URL: <https://pubmed.ncbi.nlm.nih.gov/14720013/>.
23. Gracia M C. A possible cause and corresponding treatment for inflammatory, auto-immune or auto-aggressive diseases. *Med Hypotheses.* 2007. No. 69(2). P. 395-402. URL: <https://pubmed.ncbi.nlm.nih.gov/17320308/>.
24. Zerbino D.D. General pathology of the lymphatic system. *Kyiv. Zdorovye.* 1974. 170 p.
25. Zerbino D.D. Modern pathology of the aorta: classification and main diseases. *Practical angiology.* 2010. No. 3. P. 18-23.
26. Ryabukha O. COVID-19: Multidisciplinary studies on the thyroid activity during the pandemic and post-covid processes. *Actual Problems of Medicine and Pharmacy.* 2022. Vol. 3. No. 1. P.1-25. URL: <https://doi.org/10.52914/apmp.v3i1.39>.
27. Hayduchok I.G., Shapovalova V.O., Ishcheikin K.E., Chopyak V.V., Shapovalov V.V. Pharmacoeconomic approaches for pharmacotherapy of rheumatoid arthritis. *Likars'ka sprava.* 2021. Iss.1-2. P.70-79. URL: <https://liksprava.com/index.php/journal/article/view/463>.
28. Shapovalova V. Forensic and pharmaceutical risks in the organization of pharmacotherapy of covid, post-covid and long-covid disorders. COVID-19 and vaccination practice standards. *SSP Modern Pharmacy and Medicine.* 2022. Vol. 2. No. 4. P.1–24. URL: <https://doi.org/10.53933/ssppmp.v2i4.69>.
29. Gudzenko A., Shapovalov V., Shapovalov V. et al. Forensic pharmacy: analysis of complaints about the pharmaceutical provision for privileged categories of patients in Ukraine (experimental research). *Science Review.* 2021. V. 2. Iss. 37. P. 1–6. URL: <https://rsglobal.pl/index.php/sr/article/view/1965>.
30. Shapovalov Valentyn V., Gudzenko A.O., Shapovalova V.O. et al. Clinical and pharmacological, classification and legal, nomenclature and legal distribution of medicines for pharmacotherapy of depression among combatants (F 32-33). *Health of Society.* 2021. Vol. 7. No. 4. P. 181-186. URL: <https://health-society.zaslavsky.com.ua/index.php/journal/article/view/168>.
31. Hayduchok I.G., Shapovalova V.O., Shapovalov V.V. et al. Drug control regime for the pharmacotherapy of the coronavirus disease (COVID-19) in patients with systemic diseases. *Information letter about innovations in the field of health care.* 2020. No. 225. 8 p. URL: <https://medinstytut.lviv.ua/wp-content/uploads/pdf/Informatsiynyy-lyst.pdf>.
32. Hayduchok I., Shapovalov V. Forensic pharmacy and medicine: risks for pharmacotherapy of addiction and countering of illegal circulation of psychoactive substances in the COVID-19 pandemic. 2021. *SSP Modern Pharmacy and Medicine.* Vol. 1. N. 2. P.1-28. <https://doi.org/10.53933/ssppmp.v1i2.32>.
33. Shapovalov V. (Jr.), Zbrozhek S., Gudzenko A., Shapovalova V. et al. Organizational and legal analysis of the pharmaceutical provision for the most common diseases of society. *International Journal of Pharmaceutical Sciences Review and Research.* 2018. Vol. 51. No. 1. P. 118-124. URL: <http://globalresearchonline.net/journalcontents/v51-1/18.pdf>.
34. Last year, more than 9,000 patients with bronchial asthma were registered in the Lviv region. *Varianty.* 29.05.2015. URL: <https://varianty.lviv.ua/26530-mynuloho-roku-na-lvivshchyni-zafiksuvaly-bilshe-9-tys-khvorykh-na-bronkhialnu-astmu>.
35. December 11 is World Asthma Day. Communal Healthcare Institution "Lviv Regional Information and Analytical Center of Medical Statistics". 11.12.2021. URL: https://lvivphc.org.ua/event/asthma_day_2021.
36. December 11 – World Asthma Day. Communal Healthcare Institution "Lviv Regional Information and Analytical Center of Medical Statistics". 11.12.2022. URL: https://lvivphc.org.ua/event/asthma_day_2022.
37. Bronchial asthma in winter: relief or exacerbation. *Dila.ua* 15.01.2021. URL: https://dila.ua/news/ba_zymoyu_150121.html.

38. Shapovalova V.A., Zbrozhek S.I., Shapovalov V.V. et al. Coronavirus disease pandemia 2019: growth of epidemic dangers. *Acta scientific pharmaceutical sciences*. 2020. Vol. 4. Iss. 7. P. 61–68. URL: <https://www.actascientific.com/ASPS/ASPS-04-0559.php>.
39. Shapovalova V. An Innovative multidisciplinary study of the availability of coronavirus vaccines in the world. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. No.2. P.1–17 URL: <https://doi.org/10.53933/sspmppm.v2i2.45>.
40. Shapovalova V. Monkeypox virus – new challenges of modernity: experimental organizational and legal, clinical and pharmacological studies. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. No.3. P.1–15. URL: <https://doi.org/10.53933/sspmppm.v2i3.54>.
41. Shapovalova V., Shapovalov V., Shapovalov Valentyn et al. The COVID-19 pandemic (strains "Delta", "Omicron"): particularities of study on the thematic cycle "General Pharmacy based on pharmaceutical law". *Actual problems of medicine and pharmacy*. 2022. Vol.3. No.1. P.1–18. URL: <https://doi.org/10.52914/apmp.v3i1.36>.
42. Shapovalova V. The ICD-11 for the twenty-first century: the first view from the organizational, legal, clinical and pharmacological aspects. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. No.1. P.1-13. URL: <https://doi.org/10.53933/sspmppm.v2i1.37>.
43. Ivanishyn-Hayduchok L., Shapovalova V., Shapovalov V. ICD-11: Organizational and legal, medical and pharmaceutical, social and economic issues of implementation of the program of state guarantees of medical care in 2022 in Ukraine, based on the fundamental principles of the European Union. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. No.2. P.1–14. URL: <https://doi.org/10.53933/sspmppm.v2i2.53>.
44. Shapovalov V.V. (Jr.), Shapovalova V.A., Shapovalov V.V. Development of forensic and pharmaceutical researches within the organization of pharmaceutical business, drug technology and pharmaceutical law in Ukraine concerning the turnover of controlled drugs and substances. *Health of Society*. 2021. Vol.10. No.3. P.98-106. URL: <https://doi.org/10.22141/2306-2436.10.3.2021.246351>.
45. Shapovalov V. (Jr.), Gudzenko A., Shapovalova V. et al. Forensic and pharmaceutical study of the presence of a causal link between the degree of alcohol abuse and qualification level of the respondents. *Pharmacia*. 2017. Vol.66. No.3. P. 31–39. URL: <http://bsphs.org/wp-content/uploads/2017/11/Shapovalov.pdf>.
46. Chuiev Y., Shapovalova V. Integrated ABC/VEN-analysis of drug prescriptions in pharmacotherapeutic schemes for relief of drunken forms of alcohol dependence. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. No.1. P.1-14. URL: <https://doi.org/10.53933/sspmppm.v2i1.35>.
47. Shapovalova V. Alcoholic Hepatitis: An Experimental Meta-Analysis. *SSP Modern Pharmacy and Medicine*. 2023. Vol.3. No.1. P.1-11. doi: <https://doi.org/10.53933/sspmppm.v3i1.77>. URL: <https://doi.org/10.53933/sspmppm.v3i1.77>.
48. Ryabukha O. COVID-19 Pandemic encourages to deepen the study of the thyroid gland: correlation portraits as a means of research in different directions of follicular thyrocytes activities. *SSP Modern Pharmacy and Medicine*. 2022. Vol.2. No.1. P.1-21. URL: <https://doi.org/10.53933/sspmppm.v2i1.40>.
49. Shapovalova V.A., Voloshyn P.V., Stefanov A.V. et al. Medicines for neurologists, psychiatrists and narcologists. Kh.: Fakt. 2003. 784 p.
50. Shapovalova V.A., Sosyn I.K., Butenko G.M. et al. Pharmaceutical law in narcology. Kharkov: "Fact". 2004. 800 p.
51. Gubskiy Y.I., Shapovalova V.O., Kutko I.I. et al. Medicines in psychopharmacology. K.: "Health", Kharkiv: "Torsing".1997. 288 p.
52. Sosin I.K., Chuev Yu.F., Artemchuk A.P., Shapovalova V.O. et al. Narcology: national textbook. Kharkiv, Ukraine: Kolegium. 2014. 948 p.
53. Shapovalov V.V., Shapovalova V.O., Bondarenko V.V. Evidential pharmacy regarding the forensic support of modified substances removed from illegal circulation as a measure to combat the spread of drug addiction. *Zaporozhye medical journal*. 2007. No. 3. P. 175-177.