

K. G. Shchokina, O. V. Tkachova, H. V. Bielik, M. V. Savokhina

Analysis of local anesthetics side effects and determination of ways for their minimization

National University of Pharmacy, Kharkiv

Key words: local anesthetics, pharmaceutical market of Ukraine, side effects, notification cards, evidence base

Pain is a negative psycho-emotional feeling, which is realized by systemic pain sensitivity and higher parts of the brain, signals the harmful effects of exogenous factors or the development of pathological processes in the body.

Pain is an actual problem in both social and medical aspects. According to the WHO, the scale of pain can be compared to a pandemic. Pain is the most frequent reason for patients to seek medical help [1].

Local anesthetics (LAs) are one of the groups of drugs for pain relief. LAs cause reversible loss of all types of sensitivity upon direct contact with cell membranes of peripheral nerve fibers. Modern LAs are widely used not only in anesthesiology, but also in ophthalmology, otolaryngology, etc. The widespread use of LAs in clinical practice is hindered by their rather high toxicity [2–4].

Since the introduction of LAs in clinical practice, it has been found that these drugs, although they provide pain relief during surgical and diagnostic procedures, can cause serious side effects. Adverse reactions of LAs vary from local reactions to systemic complications. Systemic side effects of LAs include motor excitement, tremors, convulsions, headache, respiratory and cardiac disturbances (tachycardia, bradycardia, decrease or increase in blood pressure, etc.), depres-

sion of the central nervous system, habituation [5–8].

The search for new ways to improve the efficiency and safety of LAs use continues to be relevant.

In general, the problem of negative effects of drugs is one of the most serious medical problems. The relevance of this problem is confirmed by numerous statistical data obtained in different countries of the world. Side effects are an integral part of the pharmacodynamics of any, even highly selective drug. Prevention and reduction of side effects of drugs is one of the most important tasks of practical medicine, which allows to improve the quality of medical care for the population.

The aim of the study was to determine the assortment of LAs on the pharmaceutical market of Ukraine, to analyze the evidence base of the effectiveness and safety of modern LAs, to monitor the side effects (SEs) of LAs in Kharkiv and Kharkiv region for the period 2018–2021, and to provide recommendations for their minimization.

Materials and methods. The methods of passive pharmacovigilance, method of spontaneous reports, method of system approach and system analysis were used in the study.

The range of LAs on the pharmaceutical market of Ukraine became the object of research. For the analysis of the assortment of LAs, the State Register of Medicinal Products of Ukraine for 2023 and the Directory of Medicines Compendium were used [9, 10].

The cases of SEs of LAs, for which notification cards were sent from the health care institutions of the city of Kharkiv and the Kharkiv region for 2018–2021 were also the object of the study.

Information on SEs of LAs was collected by means of passive pharmacovigilance (method of spontaneous reports) from notification cards according to the data of doctors, paramedics, midwives, pharmacists and nurses from all health care institutions, regardless of ownership. The notification card is a form by which medical and/or pharmaceutical trained employees and applicants report any cases of SE and/or drug ineffectiveness.

The notification cards were provided by employees of the Kharkiv pharmacovigilance department of the SE «State Expert Center of the Ministry of Health of Ukraine» from the database of the automated information system for pharmacovigilance (AISP). Notification cards about adverse reactions and/or lack of effectiveness of medicinal products during their medical use were filled out in form 137/0, in accordance with the current legislation, orders of the Ministry of Health of Ukraine dated 12.27.2006 No. 898 «On approval of the procedure for conducting pharmacovigilance» (with changes), registered in the Ministry of Justice of Ukraine on 01.29.2007 under No. 73/13340 and dated 04/05/2018 No. 620 «Instruction. Medicines. Proper practices of pharmacovigilance».

To analyze the clinical effectiveness and conditions of rational use of LAs, well-known databases were used: Cochrane Library, Trip Database, and PubMed [11].

Results and discussion. The first stage of this research was devoted to determining the place of LAs among all drugs for pain relief available on

the pharmaceutical market of Ukraine during 2023.

As of November 1, 2023, 11,608 trade names of drugs were registered in Ukraine. Of them, 3,921 are drugs of domestic manufacturers, 7,687 are foreign medicines. 532 trade names of drugs of various groups that are pain relievers are registered. The share of drugs for pharmacological pain control and pain prevention is equal to 4.6% of the entire range of drugs registered in Ukraine for this period of time. Of these, 23 are drugs for general anesthesia, 47 are opioid analgesics, 227 are non-opioid analgesics (monocomponent and combined), 190 are NSAIDs with distinct analgesic properties (monocomponent and combined), 45 names are LAs, which is 8.5% of all drugs for pain relief.

As of November 1, 2023, 9 international unpatented LAs names (45 trade marks, 65 trade names (TN) were registered in Ukraine. Of these, 16 TN preparations based on bupivacaine and procaine, 7 TN preparations based on lidocaine, 6 TN based on ropivacaine, 2 preparations containing mepivacaine, 1 – benzocaine. There are also 18 TN combined drugs on the market: 2 combinations containing lidocaine – lidocaine+prilocaine (2 TN) and lidocaine+chlorhexidine (3 TN), as well as articaine in combinations (13 TN). Combined drugs make up 27.8% of all drugs for local anesthesia registered in Ukraine. The combination of articaine with epinephrine is most common (72% of all combined LAs).

Among the registered LAs, 61.6% are drugs of domestic manufacturers, 38.5% are foreign drugs. Domestic pharmaceutical companies «Zdorovya» and «Yuriya-pharm» are leaders in the production of LAs in Ukraine (11 and 8 TN, respectively). Among foreign companies, the leader is Aspen Pharma (Ireland) (7 drugs).

Most of the LAs available on the Ukrainian market are presented in solutions for injections. But other medicinal forms of LAs are registered in Ukraine, namely, Versatis patch from Grunenthal GmbH (Germany), Dentol 7.5% gel from Pharmascience Inc. (Canada), Kategel with lidocaine, manufactured by Montavit GmbH (Austria) and Emla cream, Aspen Pharma (Sweden). Also, among all LAs on the market, 5 drugs are intended for spinal anesthesia.

The next stage of our research was devoted to the analysis of reports on SEs of LAs received from 127 health care institutions of the city of Kharkiv and the Kharkiv region for the period 2018–2021.

The results obtained showed that during the years 2018–2021, 271 notification cards were received from health care institutions of the Kharkiv region and the city of Kharkiv with cases of SEs for drugs for local anesthesia, of which 109 in 2018 and 96 in 2019, in 2020 – 45, in 2021 – 21 notification cards (Table 1).

From the analysis of the received notification cards, it can be seen that 151 (55.7%) of them are reports on SEs of LAs in men, 120 – in women (44.3%). According to the age of the patients, the registered SEs are distributed as follows: 33 notification cards from patients under 10 years old, which is 12.2% of the total amount of information. 18 notification cards belong to patients aged 11 to 20, which is equal to 6.6% of the total number of cards. 84 notification cards came from

patients aged 21 to 40 (31%). 79 notification cards – from patients in the age range of 41–60 years (29.2%). 55 cards – from patients aged 61 to 80 (20.3%). 2 cards were received from patients over 80 years old, which is 0.7% of the total number of messages.

The analysis of the notification cards revealed that among LAs in 2018, 2019, 2020, the most SEs were registered for lidocaine preparations, in 2021 – for lidocaine containing drugs and for the combination of articaine and epinephrine.

Monitoring of SEs of LAs for the period 2018–2021 became the next stage of our research (Table 2).

SEs monitoring of LAs for the period 2018–2021 showed that the largest number of there was registered in the form of dizziness and weakness (55.8%). The following adverse reactions were also recorded: edema, itching, hyperemia at the site of application (12.1%), decrease in blood pressure (12.4%), decrease in heart rate (3.3%), increase in blood pressure (2.9%), colds weat (4.7%), nausea, tinnitus (0.8% each), headache, cyanosis of lips, skin (0.5% each). These SEs did not require additional hospitalization and did not cause patient disability.

SEs of LAs drugs, recorded during the analysis of message cards, coincide with the literature data [12–15]. As for lidocaine medicines, which received the most reports of SEs, one of the explanations may be that lidocaine containing drugs are the leaders of the Ukrainian pharmaceutical market.

Table 1

Side effects of local anesthetics during 2018–2021 in health care institutions of Kharkiv and Kharkiv region

Number of notification cards			
2018	2019	2020	2021
109	96	45	21

Table 2

Monitoring of the frequency of side effects of local anesthetics during 2018–2021 in health care institutions of Kharkiv and Kharkiv region

Side effect	The number of registered side effects			
	2018	2019	2020	2021
Dizziness, weakness	86	73	38	15
Swelling, itching, hyperemia at the site of application	16	20	4	6
Decrease in blood pressure	30	13	4	–
Increase in blood pressure	7	4	–	–
Headache	1	1	–	–
Tinnitus	1	–	2	–
Decreased heart rate	12	1	–	–
Skin rashes	1	–	1	–
Chest pain	2	–	–	–
Nausea	–	2	1	–
Cyanosis of lips, skin	–	2	–	–
Cold sweat	11	7	–	–
Total number of side effects reports	167	123	50	21

Well-known data bases were used to analyze the clinical effectiveness and conditions of rational use of LAs in order to prevent/minimize their side effects: Cochrane Library, Trip Database, PubMed. These databases contain systematized primary or secondary information on a specific clinical issue: the effectiveness and safety of various medical technologies [11].

According to the data of 12 systematic reviews, it was determined that the most serious SEs of LAs include motor excitement, tremors, convulsions, headache, impaired breathing and heart function (tachycardia, bradycardia, decrease or increase in blood pressure, etc.) [16–19]. At present, lidocaine and bupivacaine remain the most popular drugs for anesthesia. They belong to amide LAs with good solubility in fats [20, 21]. Lidocaine is a

derivative of xylidine, acts stronger and longer than procaine, causes drowsiness and depresses the central nervous system, has an antiarrhythmic effect [22]. Bupivacaine is more potent than lidocaine. Racemic bupivacaine is characterized by extremely high cardio- and local toxicity due to the stereospecificity of the drug, the S(–)-enantiomer has a significantly lower cardiodepressant effect than the R(+)-enantiomer. Current long-acting LAs are ropivacaine and levobupivacaine. Ropivacaine is characterized by significantly lower systemic toxicity compared to bupivacaine [23].

Reducing of LAs toxicity can be achieved by different ways. First, the blockade of peripheral nerves under ultrasound control allows to reduce doses of LAs while maintaining the effectiveness of anesthesia. The second

direction is the use of modern LAs ropivacaine and levobupivacaine as the least toxic anesthetics [24, 25]. The next direction is associated with the addition to LAs of substances with vasoconstrictive properties, such as epinephrine (adrenaline), dexamethasone, dexmedetomidine and others [26, 27]. The use of LAs combinations also provides a safety advantages by reducing the dose of long-acting LAs, which are potentially more cardiotoxic than short-acting LAs. Combinations of LAs are also used for peripheral nerve blocks to obtain faster action from short-acting LAs and to prolong the duration of action due to long-acting LAs. It was demonstrated a significant reduction in the latent period of anesthesia when comparing combinations with long-acting LAs [28]. For example, the combination of bupivacaine and lidocaine allows to reduce the dose of bupivacaine by 3 times, which reduces the likelihood of toxic complications of lead anesthesia. Thus, the clinical use of the proposed combination of drugs shortens the duration of the latent period compared to bupivacaine and provides a sufficient duration of postoperative analgesia. A promising way to reduce the side effects of LAs is also the use of a composition of bupivacaine and clonidine, which improves the indicators of the prooxidant-antioxidant balance [29, 30].

Conclusions

1. The range of drugs for local anesthesia on the modern pharmaceutical market of Ukraine is quite wide. In 2023, 65 trade names of local anesthetics were registered, which

include 9 international non-proprietary names. The leaders are bupivacaine and procaine, there are 16 trade names of drugs based on them on the market. The second place is occupied by articaine in combination with epinephrine (13 drugs), the third place is lidocaine (7 drugs). Among all local anesthetic drugs, 27.8% are combined dosage forms. The range of products of domestic and foreign manufacturers is, respectively, 61.6% and 38.5% of the total number of medicines of this group on the market. Therefore, it can be assumed that consumers of local anesthetics do not prefer only drugs of domestic manufacturers, but also actively use foreign drugs.

2. The analysis of notification cards with cases of side effects for 4 years showed that the majority of adverse reactions in the form of dizziness, weakness, changes in blood pressure, heart rate, swelling, itching, hyperemia at the site of application were recorded when lidocaine drugs use, which are the most demanded and popular among doctors.
3. According to the data of systematic reviews, the main directions for reducing the side effects of local anesthetics have been established, such as administration under ultrasound control, the use of the least toxic modern anesthetics ropivacaine and levobupivacaine, the addition of substances with vasoconstrictive properties to the anesthetic solution, the use of combinations of long-acting and short-acting anesthetics.

1. Колесник Ю. М., Чекман І. З., Беленічев І. Ф. Фармакологія з основами патології. Вінниця : Нова книга, 2021. 472 с.
2. Місцеві анестетики: сучасний погляд. Ю. Л. Кучин, М. М. Пилипенко, Ю. І. Налапко, Р. Крегг. *Медицина болю*. 2016. Т. 3 (3). С. 7–18.
3. Evaluation of adverse reactions to local anesthetics: experience with 236 patients. Y. Bercum, A. Ben-Zvi, Y. Levy et al. *Ann. Allergy Asthma Immunol.* 2003. V. 91. P. 342–345.

4. Becker D. E., Reed K. L. Essentials of local anesthetic pharmacology. *Anesth. Prog.* 2006. V. 53 (3). P. 98–109.
5. Becker D. E., Reed K. L., Becker D. E. Similar articles. Local anesthetics: review of pharmacological considerations. *Anesth. Prog.* 2012. V. 59 (2). P. 90–101.
6. Зайков С. В., Кайдашев І. П., Гуменюк Г. Л. Проблема гіперчутливості до місцевих анестетиків. *Infusion & Chemotherapy.* 2020. № 3. С. 43–51.
7. Brull S. J. Lipid emulsion for the treatment of local anesthetic toxicity: patient safety implications. *Anesth. Analg.* 2008.V. 106. P. 1337–1339.
8. Mather L. E., Copeland S. E., Ladd L. A. Acute toxicity of local anesthetics: underlying pharmacokinetic and pharmacodynamic concepts. *Reg. Anesth. Pain Med.* 2005. V. 30. P. 553–566.
9. Державний реєстр лікарських засобів України. URL: <http://www.drz.com.ua/>– доступ вільний.
10. Довідник лікарських препаратів Компендіум. URL: <https://compendium.com.ua>.
11. База даних доказової медицини. Фармацевтична енциклопедія. URL: <https://www.pharmacy-clopedia.com.ua/article/1822/baza-danixdokazovoi-medicini>.
12. Фармакологія за Рангом і Дейлом: 9-е вид.: у 2 т. Т. 1. Джеймс М. Ріттер, Род Флавер, ГремГендерсон, Юн Конг Лоук, Девід Мак'юен, Гамфрі П. Ранг. Всеукраїнське спеціалізоване видавництво «Медицина», 2021. 600 с.
13. Harvey M., Cave G. Bupivacaine-induced cardiac arrest: fat is good – is epinephrine really bad? *Anesthesiology.* 2009. V. 111. P. 467–469.
14. Successful resuscitation after ropivacaine and lidocaine-induced ventricular arrhythmia following posterior lumbar plexus block in a child. H. Ludot, J. Tharin, M. Belouadah et al. *Anesth. Analg.* 2008. V. 106 (5). P. 1572–1574.
15. Venemalm L., Degerbeck F., Smith W. IgE-mediated reaction to mepivacaine. *J. Allergy Clin. Immunol.* 2008. V. 121 (4). P. 1058–1059. <https://doi.org/10.1016/j.jaci.2007.12.1154>.
16. Two randomized, double-masked, placebo-controlled studies of the local anesthetic effect of articanine ophthalmic solution. V. H. Gonzalez, D. L. Wirta, M. Uram et al. *Clin. Ophthalmol.* 2023. V. 10 (17). P. 1357–1365. <https://doi.org/0.2147/OPHTH.S409241>.
17. Injectable local anaesthetic agents for dental anaesthesia. G. St. George, A. Morgan, J. Meechan et al. *Cochrane Database of Systematic Reviews.* 2018. Iss. 7. Art. No.: CD006487.
18. Wound infiltration with local anaesthetic agents for laparoscopic cholecystectomy. S. Loizides, K. S. Gurusamy, M. Nagendran et al. *Cochrane Database of Systematic Reviews.* 2014. Iss. 3. Art. No.: CD007049.
19. Topical anaesthetics for pain control during repair of dermal laceration. B. O. Tayeb, A. Eidelman, C. L. Eidelman et al. *Cochrane Database of Systematic Reviews.* 2017. Iss. 2. Art. No.: CD005364.
20. Regis Fuzier, Maryse Lapeyre-Mestre. Safety of amide local anesthetics: new trends. *Expert Opin. Drug Saf.* 2010. V. 9 (5). P. 759–769. <https://doi.org/10.1517/14740331003789373>.
21. Safety of Lidocaine during wide-awake local anesthesia no tourniquet for distal radius plating. Shalimar Abdullah, Muhamad Fitri Tokiran, Amir Adham Ahmad et al. *J. Hand Surg. Glob. Online.* 2023. V. 5 (2). P. 196–200. <https://doi.org/10.1016/j.jhsg.2022.12.003>.
22. Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section. B. L. Sing, F. J. Siddiqui, W. L. Leong et al. *Cochrane Database of Systematic Reviews.* 2016. Iss. 9. Art. No.: CD005143.
23. Comparison between ropivacaine and bupivacaine in deep topical fornix nerve block anesthesia in patients undergoing cataract surgery by phacoemulsification. Anshika Kashyap, Rahul Varshney, Govind Singh Titiyal, Ajay Kumar Sinha. *Indian J. Ophthalmol.* 2018. V. 66 (9). P. 1268–1271. https://doi.org/10.4103/ijo.IJO_100_18.
24. Nader A., Kendall M. C., De Oliveira G. S. Jr. A dose ranging study of 0.5% bupivacaine or ropivacaine on the success and duration of the ultrasound guided, nerve-stimulator-assisted sciatic nerve block: a double-blind, randomized clinical trial. *Reg. Anesth. Pain Med.* 2013. V. 38. P. 492–502.
25. Лісний І. І., Закальська Х. А. Місце ропівакаїну у сучасній регіонарній анестезії. *Клінічна онкологія.* 2021. V. 11, № 1 (41). С. 1–5.
26. Decreasing the pain of local anesthesia: a prospective, double-blind comparison of buffered, pre-mixed 1% lidocaine with epinephrine versus 1% lidocaine freshly mixed with epinephrine. C. A. Burns, G. Ferris, C. Feng et al. *J. Am. Acad. Dermatol.* 2006. V. 54 (1). P. 128–131. <https://doi.org/10.1016/j.jaad.2005.06.043>.
27. Adrenaline with lidocaine for digital nerve blocks. H. Prabhakar, S. Rath, M. Kalaivani, N. Bhandari. *Cochrane Database of Systematic Reviews.* 2015. Iss. 3. Art. No.: CD010645.
28. Taha A. M., Abd-Elmaksoud A. M. Lidocaine use in ultrasound-guided femoral nerve block: what is the minimum effective anaesthetic concentration (MEAC90)? *Br. J. Anaesth.* 2013. V. 110. P. 1040–1044.

-
29. A comparative analysis of local anesthetics: injection associated pain and duration of anesthesia. A. Moses, S. Klager, A. Weinstein et al. *J. Drugs Dermatol.* 2023. V. 22 (4). P. 364–368. <https://doi.org/10.36849/JDD.5183>.
30. Козловський Ю. К., Макогончук А. В., Козловська І. Ю. Досвід застосування місцевих анестезуючих комбінацій. *Медицина невідкладних станів.* 2021. Т. 4 (17). С. 65–68.

Конфлікт інтересів відсутній.

K. G. Shchokina, O. V. Tkachova, H. V. Belik, M. V. Savokhina
Analysis of local anesthetics side effects and determination of ways for their minimization

According to the World Health Organization (WHO), the development of side effects of drugs is one of the serious medical problems. The relevance of this problem is proven by numerous statistical data obtained in different countries of the world.

The aim of the study was to determine the assortment of local anesthetics (LAs) on the pharmaceutical market of Ukraine, to analyze the evidence base of the effectiveness and safety of modern LAs, to monitor the side effects (SEs) of LAs in Kharkiv and Kharkiv region for the period 2018–2021, and to provide recommendations for their minimization.

The methods of passive pharmacovigilance, method of spontaneous reports, method of system approach and system analysis were used in the study. To analyze the clinical effectiveness and conditions of rational use of LAs, well-known data bases were used: Cochrane Library, Trip Database, and PubMed. These databases contain systematized primary or secondary information on a specific clinical issue: the effectiveness and safety of various medical technologies.

The results of the analysis of the assortment of LAs on the pharmaceutical market of Ukraine showed that in 2023, based on 9 international non-patented names of LAs, 65 trade names were presented. Bupivacaine and procaine drugs (16 trade names each) and articaine drugs in combinations (13 trade names) are market leaders.

The results of the analysis of notification cards with cases of SEs for 4 years revealed that the majority of them in the form of dizziness, weakness, changes in blood pressure, heart rate, edema, itching, hyperemia at the site of application were recorded when using lidocaine drugs, which are the most in demand and popular among doctors.

According to the data of systematic reviews, the main directions for reducing the side effects of LAs have been established, such as administration under ultrasound control, the use of the least toxic modern anesthetics ropivacaine and levobupivacaine (not available on the Ukrainian market), the addition of substances with vasoconstrictive properties to the anesthetic solution, the use of combinations of long-acting and short-acting anesthetics.

The results obtained can be used by practicing doctors and health care organizers to optimize LAs.

Key words: local anesthetics, pharmaceutical market of Ukraine, side effects, notification cards, evidence base

K. G. Щокіна, О. В. Ткачова, Г. В. Белік, М. В. Савохіна
Аналіз побічної дії місцевих анестетиків і визначення шляхів їхньої мінімізації

За даними Всесвітньої організації охорони здоров'я, розвиток побічної дії ліків є однією з серйозних медичних проблем. Актуальність цієї проблеми підтверджується численними статистичними даними, які отримані в різних країнах світу.

Мета дослідження – аналіз асортименту на фармацевтичному ринку України препаратів для місцевої анестезії, доказової бази щодо їхньої клінічної ефективності та безпечності, моніторинг побічних ефектів, що викликали місцеві анестетики в Харкові та Харківській області в 2018–2021 роках, і надання рекомендації щодо мінімізації проявів побічних ефектів препаратів даної групи.

У дослідженні використовували методи спонтанних повідомлень, маркетингового аналізу, системного підходу та системного аналізу. Для аналізу клінічної ефективності та умов раціонального застосування місцевих анестетиків використовували відомі бази даних доказової медицини: Cochrane Library, Trip Database, PubMed. Ці бази даних містять систематизовану первинну та вторинну інформацію з конкретної клінічної проблеми щодо ефективності та безпеки різних медичних технологій.

Результати аналізу асортименту місцевих анестетиків на фармацевтичному ринку України показали, що в 2023 році на основі 9 міжнародних непатентованих найменувань місцевих анестетиків було представлено 65 торгових найменувань. Лідерами на ринку є препарати бупівакаїну та прокаїну (по 16 торгових найменувань) та препарати артикаїну в комбінаціях (13 торгових найменувань).

Результати аналізу карт-повідомлень з випадками побічних реакцій за 4 роки виявили, що більшість з них у вигляді запаморочення, слабкості, змін артеріального тиску, частоти серцевих скорочень, набряку, свербіжжю, гіперемії в місці застосування зафіксовані в разі застосування препаратів лідокаїну, які є найзатребуванішими та популярними серед лікарів.

За даними систематичних оглядів встановлено основні напрями зменшення побічних ефектів місцевих анестетиків, такі як введення під ультразвуковим контролем, застосування найменш токсичних сучасних анестетиків ропівакаїну й левобупівакаїну (відсутні на ринку України), додавання до розчину анестетику речовин зі судинозвужувальними властивостями, використання комбінацій анестетиків тривалої та короткої дії.

Отримані результати дослідження можуть бути використані лікарями-практиками та організаціями охорони здоров'я для оптимізації місцевої анестезії.

Ключові слова: місцеві анестетики, побічна дія, фармацевтичний ринок України, карти-повідомлення, доказова база

ORCID ID авторів:

Щокіна К. Г. (ORCID ID 0000-0003-3297-5999);

Ткачова О. В. (ORCID ID 0000000346460400);

Бєлік Г. В. (ORCID ID 0000-0001-7207-2036);

Савохіна М. В. (ORCID ID 0000-0002-0143-9707).

Надійшла: 4 січня 2024 р.

Прийнята до друку: 20 березня 2024 р.

Контактна особа: Ткачова Оксана Віталіївна, доктор фармацевтичних наук, кафедра фармацевтичного менеджменту та маркетингу, Національний фармацевтичний університет, буд. 4, вул. Валентинівська, м. Харків, 61168. Тел: + 38 0 99 024 72 14.
Електронна пошта: tkachevaov@gmail.com