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MARKETING STUDY OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS FOR THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER IN MILITARY SERVANTS AND WAR VETERANS

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The aim of the work: *to present the results of a marketing study of medicinal products of the ATC classification group N06AB "Selective serotonin reuptake inhibitors" (SSRIs) in terms of registration and legal status, the state of the wholesale and retail market, presence in socio-economic regulatory lists of medicinal products, as well as to evaluate the results of an anonymous survey of doctors regarding the prescription of SSRIs to military personnel and war veterans with post-traumatic stress disorder (PTSD).*

Materials and methods. *Methods such as analysis, synthesis, comparison, specification, systematization, generalization, and reliability assessment were used; an anonymous survey of 35 psychiatrists and 25 neurologists was conducted regarding the prescription of drugs for patients with PTSD.*

Results and discussion. *It was found that SSRIs should be considered as first-line pharmacotherapy for military personnel with PTSD. At the same time, escitalopram, which, according to the literature, demonstrates the best safety and efficacy indicators, which was preferred by 97 % of the surveyed doctors, the market of which showed the greatest growth in terms of assortment and which was most numerously included in the List of Drugs Subject to Reimbursement, remains absent from the updated Unified Clinical Protocol for the Treatment of PTSD.*

Conclusions*. 100 % of doctors confirmed the choice of SSRIs, among which, with a probability of type I error α=0.05, a reliable probability of p≥0.95 regarding the unanimity of responses, psychiatrists most often prescribed escitalopram and sertraline, neurologists – citalopram and escitalopram, in general – escitalopram.*

As of 01.10.2024, 45 trade names of SSRIs were registered in Ukraine (4 – fluoxetine, 1 – citalopram, 7 – paroxetine, 9 – sertraline, 2 – fluvoxamine, 22 – escitalopram), 80 % of the drugs were of foreign origin, 20 % of which were manufactured to order by domestic manufacturing companies. Imported drugs came from 15 countries, most of them – from India (28 %); among 9 domestic companies, Pharma Start LLC supplies the largest number of medicines (33 %).

It was found that currently the lowest prices for drugs in Ukraine are offered by the drug booking service Tabletky.UA. The state reimburses the cost of PTSD treatment with the most affordable drugs paroxetine and sertraline (1 trade name each), fluoxetine (3), escitalopram (5). Therefore, given the results of the study, it is recommended to include escitalopram in the Unified Clinical Protocol of Primary and Specialized Medical Care "Acute Stress Reaction. PTSD. Adaptation Disorders"

Keywords*: post-traumatic stress disorder, selective serotonin reuptake inhibitors, marketing analysis, pharmaceutical market, reimbursement program, escitalopram*

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1. Introduction

Post-traumatic stress disorder (PTSD) is a mental health disorder that occurs as a result of a traumatic event and can lead to disability; it is characterized by the direct or indirect impact of a traumatic event which triggered an intense fear response, and later transformed into a dysfunction lasting more than 1 month with a triad of symptoms: recurrent re-experiencing of the trauma, numbness/avoidance behaviour, and persistent hyperarousal [1, 2].

A full-scale war is ongoing in Ukraine. Military personnel and civilians are exposed to stress every day. Some military personnel and veterans, mostly those who were directly in the combat zone, have PTSD and face its consequences, which are difficult to overcome without the help of loved ones and qualified psychotherapeutic assistance.

In 1983, the U.S. Congress mandated the United States Department of Veterans Affairs (VA) and the United States Department of Defense (DoD) to conduct a study for a better understanding of the psychological consequences experienced by Vietnam War participants. The study revealed that approximately 15 % of the 2.7 million Americans who served in this war suffered from PTSD [3].

Selective serotonin reuptake inhibitors (SSRIs) represent a major psychopharmacological breakthrough and mark a new era in the development of psychotropic medications. During the development of SSRIs, researchers discovered a range of non-tricyclic agents with amine uptake inhibitory properties, acting on serotonergic neurons with significant differences in efficacy. SSRIs were specifically designed to inhibit the neuronal serotonin

uptake pump. This property is shared with tricyclic antidepressants (ADs), but unlike them, SSRIs do not affect other neuroreceptors or fast sodium channels. SSRIs have been recognized as effective in treating social anxiety disorder by reducing overall social anxiety levels and improving the general clinical condition in PTSD. At the same time, no single antidepressant can be considered a universal standard recommendation for every patient. However, for the vast majority of individuals with PTSD, this group of antidepressants should be regarded as first-line therapeutic agents [1].

Currently, six international non-proprietary names (INNs) of medications classified under the ATC code N06AB (Anatomical Therapeutic Chemical Classification System) are registered in Ukraine. These are: Fluoxetine (N06AB03), Citalopram (N06AB04), Paroxetine (N06AB05), Sertraline (N06AB06), Escitalopram (N06AB10), and Fluvoxamine (N06AB08) [4].

In modern domestic psychopharmacology, SSRIs are used in accordance with the updated Unified Clinical Protocol for Primary and Specialized Medical Care "Acute Stress Reaction. Post-Traumatic Stress Disorder. Adaptation Disorders," approved by the Order of the Ministry of Health of Ukraine No. 1265 dated July 19, 2024. This protocol was developed considering the latest advancements in evidence-based medicine and emphasizes the specifics of diagnosing and treating patients with PTSD [5].

According to the recommendations of this protocol, antidepressants are appropriate for treating PTSD in adults when psychotherapy has been ineffective. Additionally, they should be used when the patient [5]:

– refuses to participate in trauma-focused psychotherapy;

– is not stable enough to begin psychotherapy;

– experiences a large number of psychological symptoms of comorbid disorders, which may significantly worsen during psychotherapy.

The therapeutic intervention complex should include priority approaches focused on trauma, pharmacotherapy, psychosocial rehabilitation, and more. When using pharmacological agents, preference should be given to SSRIs (Paroxetine and Sertraline are recommended at the stage of primary care, while Paroxetine, Sertraline, and Fluoxetine are appropriate at the stage of specialized medical care) [5].

The list of SSRIs recommended by the Unified Clinical Protocol for Primary and Specialized Medical Care and the Clinical Practice Guidelines (CPG) developed by the VA/DoD for treating patients with PTSD and acute stress disorder, updated in 2023, coincide. The CPG for PTSD pharmacotherapy recommends Paroxetine (N06AB05) and Sertraline (N06AB06) from the SSRIs group or Venlafaxine (N06AX16) from the Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) group [6, 7].

Pharmacological approaches to treating PTSD patients are examined in studies by M. Hoskins et al. (2021). They justify the use of Fluoxetine, Paroxetine, Sertraline from the SSRIs group and Quetiapine (N05AH04) from the antipsychotic group as potential monotherapy agents for PTSD [8].

At the same time, a review of the World Health Organization's Model List of Essential Medicines (23rd edition as of 2024) revealed that among the SSRIs group, only Fluoxetine is included as a treatment for depressive disorders, anxiety disorders, and obsessive-compulsive disorders [9].

Scientific results analyzing the efficacy, safety, and marketing indicators of the SSRIs group, conducted by Professors O. Mishchenko and N. Bezdytko (2023) based on meta-analyses published in international journals, are available in the public domain [10]. The authors concluded that Escitalopram has the highest index of efficacy, safety, and accessibility among SSRIs. This medication impacts all key pathways of PTSD pathogenesis, combines antidepressant and neurotrophic activities, and its pharmacodynamics and pharmacokinetics are not age dependent. Escitalopram is administered in a fixed dose, has a minimal incidence of side effects, can be safely used in comorbid patients, and its use is pharmacoeconomically justified [10].

The increase in the consumption of AD for the treatment of patients with PTSD in recent years has been observed at the global level due to the consequences of the COVID-19 pandemic. Thus, as of 2022, according to the National Institute of Mental Health, approximately 7.7 million people in the United States suffer from PTSD [11]. According to another source [12], the global market for AD for the treatment of PTSD in 2021 was approximately 915.8 million US dollars, with North America leading the way with a revenue share of 57.83 %. According to forecasts, the global market for AD for the treatment of patients with PTSD has a chance to grow to 1.57 billion US dollars by 2030 [12].

In Ukraine, before the full-scale invasion, a culture of drug consumption was not developed, and Ukrainians took these drugs 10 times less often than on average in the world. And even now, despite the growth of the drug market due to the war, compatriots consume them several times less than the world average (I. Gorlova, 2023) [13]. Nevertheless, according to the analytical company SMD, in the first half of 2023, compared to the first half of 2022, in the SSRIs segment, there was an increase in drug sales both in packages and in monetary terms, namely: by 13.5 % and 22.7 %, respectively, for escitalopram, by 7 % and 13.1 % for paroxetine, and by 5 % and 8.8 % for sertraline [13].

Marketing research on the drug market for the treatment of PTSD in Ukraine for the period 2013–2017 were conducted by A. Ostapenko and O. Yakovleva on the analysis of the dynamics of AD registration and their economic attractiveness [14]. However, in recent years, and especially this year, the socio-economic accessibility of N06AB group drugs has changed significantly, as their legal status in Ukraine has changed.

This work was devoted to the analysis of these changes, which aimed to analyze the pharmaceutical market (PM) of Ukraine in the segment of the ATC classification group N06AB "Selective serotonin reuptake inhibitors" in terms of the registration and legal status of drugs, the state of their wholesale and retail markets, and

their presence in socio-economic regulatory lists of drugs (SERLD), and also conduct an anonymous survey of doctors regarding the prescription of drugs to military personnel and war veterans with PTSD.

2. Research planning (methodology)

To achieve this goal, an algorithm was developed that included seven stages.

At the first stage, approaches to pharmacotherapy of patients with PTSD in Ukraine were developed in comparison with global trends, especially regarding the treatment of military personnel. Practical recommendations developed by the US Departments of Veterans Affairs and Defence were selected for analysis, since this country had experience in providing assistance to military personnel and veterans of the Vietnam War. An indicative list of essential medicines developed by WHO was developed, under the ATC code N06AB "Selective serotonin reuptake inhibitors". Trends in the pharmaceutical market of drugs of the N06AB group in the world and in Ukraine were studied.

At the second stage, an anonymous survey of 35 psychiatrists and 25 neurologists was conducted on the prescription of SSRIs to patients with PTSD in modern conditions and the reliability of the results was assessed.

At the third stage, the dynamics of registration of SSRIs in Ukraine over 24 years (2000–2024) with a step of 6 years was clarified and the current registration status of the drugs as of 01.10.2024 was studied. The study sample consisted of single-component drugs of the N06AB group "Selective serotonin reuptake inhibitors" by ATC codes. An analysis of the studied trade names of SSRIs drugs by country of origin, domestic manufacturing companies, dosage form (DF), and dosage was conducted.

At the fourth stage of the study, the presence of SSRIs in the wholesale segment of the pharmaceutical market of Ukraine as of the first decade of October 2024 and the processing of wholesale prices of drugs were analyzed.

At the fifth stage, data processing of the retail segment of the pharmaceutical market of Ukraine was carried out according to data from two drug search and reservation services: Apteka.UA and Tabletky.UA. A comparison of retail prices for each trade name of representatives of the SSRIs group was made between the indicated Internet resources. A comparative analysis of retail prices of different manufacturers as of 10.10.2024 in Kyiv was made for those dosages and forms of release of representatives of the SSRIs group that are most often used by patients according to doctors' prescriptions.

At the sixth stage, the presence of registered drugs of the N06AB group "Selective serotonin reuptake inhibitors" in the socio-economic regulatory lists of drugs in Ukraine was investigated, namely the National List of Essential Medicines (EML) for which state price regulation is established, the State Formulary of Drugs, the Register of Wholesale Prices for Drugs, and the List of Drugs subject to reimbursement under the program of state guarantees of medical care for the population.

At the seventh stage of the work, a graphical representation of the research results was carried out, its presentation was made, relevant conclusions were drawn, and recommendations were provided.

3. Materials and methods

To assess the status of registration, its dynamics, analyze the range of representatives of the SSRIs group, the wholesale and retail share of the domestic pharmaceutical market of drugs, and the presence in SERLD in Ukraine, the State Register of Drugs of Ukraine [4], Compendium [15], the specialized online publication "Apteka Weekly" – Apteka.UA [16], the drug search and reservation service in pharmacies Tabletky.UA [17], the National List of EML [18], the State Formulary of Medicines (DFLZ) [19], the Register of Wholesale and Retail Prices (ORP) for Drugs [20], and the List of Drugs Subject to Reimbursement under the State Health Care Guarantees Program [21]. The work also used 60 anonymous questionnaires from doctors, of whom 35 people (58.3 %) were psychiatrists and 25 (41.7 %) were neurologists.

The study used methods such as analysis, synthesis, comparison, specification, systematization, generalization, and reliability assessment [22].

4. Results and discussion

As indicated by the literature, there is a sufficient number of drugs whose effectiveness has been studied in patients with various types of PTSD. Most of them are antidepressants [1, 5, 10, 23]. Therefore, during the anonymous survey, doctors were asked the question: "Which subgroup from the group N06A "Antidepressants" do you prescribe for PTSD?" The distribution of their answers by medical specialties (psychiatrists, neurologists, together) is shown in Table 1.

Table 1

Assessment of priority among group N06A "Antidepressants" in prescriptions for military patients with PTSD based on the results of an anonymous questionnaire of doctors

No.	Subgroup of antidepressants	Percentage of doctors who prescribed drugs, %		
		Psychiatrists (*n*=35)	Neurologists (*n*=25)	All respondents (*n*=60)
1	N06AA «Non-selective monoamine reuptake inhibitors»	0	0	0
2	N06AB «Selective serotonin reuptake inhibitors»	100	100	100
3	N06AF «Monoamine oxidase inhibitors, non-selective»	0	0	0
4	N06AG «Monoamine oxidase A inhibitors»	0	0	0
5	N06AX «Other antidepressants»	74.3	0	43.8

Analyzing (Table 1), we state that 100 % of psychiatrists and 100 % of neurologists noted that SSRIs (N06AB) are prescribed to military personnel with PTSD, in addition, 74.3 % of psychiatrists (26 out of 35 people) confirmed the practice of prescribing drugs from the subgroup "Other an-

tidepressants" (N06AX). At the same time, neurologists prefer only SSRIs. These results coincide with the literature data [1, 5, 23], since SSRIs have the largest evidence base for use in PTSD. They have been most fruitfully studied in randomized controlled trials and have shown the highest effectiveness among other drugs [10].

Within the subgroup N06AB "Selective serotonin reuptake inhibitors", the general preferences of doctors (n=60) are shown in Fig. 1 (each respondent was able to choose those drugs for which he has a practice of prescribing).

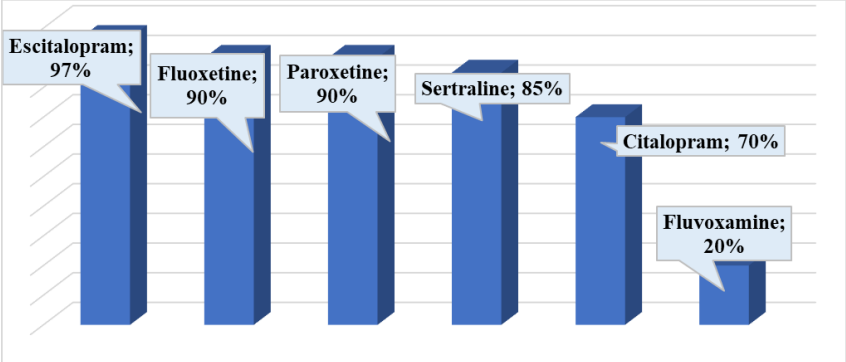

Fig. 1. Distribution of drugs of the N06AB group "Selective serotonin reuptake inhibitors" by INN according to the degree of leadership in the practice of prescribing doctors (n=60) for patients with PTSD

Within medical specialties, individual INNs of this subgroup were distributed as follows by the percentage of specialists who had experience in prescribing them:

– psychiatrists (n=35) – N06AB03 Fluoxetine (100.0 %)→N06AB05Paroxetine(100.,0 %)→N06AB06 Sertraline (100.0 %)→N06AB10 Escitalopram (100.0 %)→N06AB04 Citalopram (82.9 %)→N06AB08 Fluvoxamine (20.0 %);

– neurologists (n=25) – N06AB10 Escitalopram (92.0 %)→N06AB03 Fluoxetine (76.0 %)→N06AB05 Paroxetine (76.0 %)→N06AB06 Sertraline (64.0 %)→N06AB04 Citalopram (52.0 %)→N06AB08 Fluvoxamine (20.0 %).

To further study the priority of SSRI INNs among physicians who had experience in prescribing the drug, respondents were also asked to indicate the frequency of use of each INN on a scale from 0 to 10, where 0 is "not used" and 10 is "most often used" (Table 2).

The probability of unanimity of the answers provided by the participants of the anonymous questionnaire was studied by determining the concordance coefficient, the value of the Fisher test, and the test distributed according to the c^2 distribution (Table 3).

The results of statistical analysis of the data from the doctor survey, presented in Table 2 and Table 3, allow us to state that:

– for PTSD in military personnel, among antidepressants from the subgroup N06AB SSRIs by INN, psychiatrists most often prescribed Escitalopram and Sertraline, neurologists – Citalopram and Escitalopram, and doctors in general – Escitalopram, and unanimously prescribed with the least frequency – Fluvoxamine;

– the respondents' assessment of antidepressants from the subgroup N06AB SSRIs by INN regarding the frequency of their prescription according to the answers to the questionnaire questions was unanimous (probability of type I error α=0.05, reliable probability p^3=0.95).

Citalopram, which is the leader in the ranks of neurologists, is a racemic mixture of 2 enantiomers – R-(-)-citalopram and S-(+)-citalopram in its chemical composition. At the same time, only the second isomer exhibits pharmacological action, which, as a separate INN Escitalopram, was approved for clinical use 12 years later than its predecessor Citalopram [1, 23].

At the next stage of the work, the dynamics and current state of state registration of INNs N06AB03 Fluoxetin, N06AB04 Citalopram, N06AB05 Paroxetin, N06AB06 Sertraline, N06AB08 Fluvoxamine, N06AB10 Escitalopram by trade names (TN) in Ukraine were studied [4] (Fig. 2).

Table 2

Ranks of antidepressants from the subgroup N06AB SSRIs by INN according to respondents' assessment

Antidepressants from subgroup N06AB SSRIs by INN	Groups of study participants		
	Psychiatrists (n=35)	Neurologists (n=25)	All respondents (n=60)
	Final ranks		
Fluoxetine	3	3	3
Citalopram	5	1	2
Paroxetine	4	4	5
Sertraline	2	5	4
Fluvoxamine	6	6	6
Escitalopram	1	2	1

Table 3

Consistency in respondents' assessment of antidepressants from the subgroup N06AB SSRIs by INN regarding the frequency of their prescription ($p^3$0.95, α=0.05)

Criteria, conclusions		Groups of study participants		
		Psychiatrists (n=35)	Neurologists (n=25)	All respondents (n=60)
		The meaning of the criteria, conclusions		
Concordance coefficient		0.480	0.340	0.372
Fisher's test value	f	31.325	12.369	34.981
	f^*	2.282	2.311	2.253
Conclusions		If there is inequality $f>f^*$, then the assessment is unanimous		
The value of the criterion distributed according to the χ^2-distribution	χ^2	83.917	42,512	111,664
	χ^{2*}	11.071		
Conclusions		If there is inequality $\chi^2>\chi^{2*}$, then the assessment is unanimous		

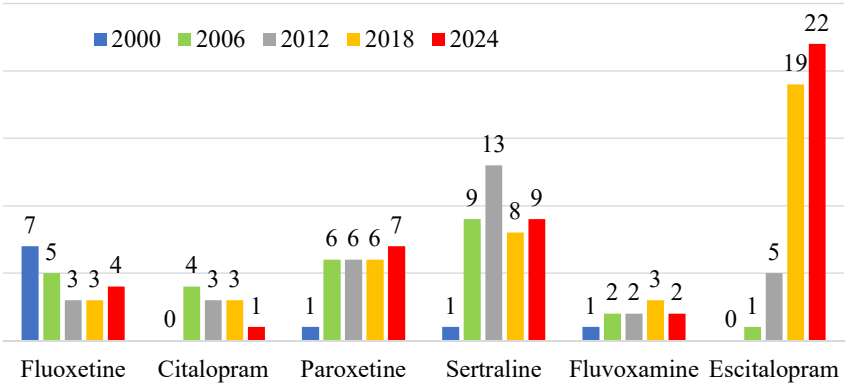

Fig. 2. Dynamics of the number of registered TN drugs of the N06AB SSRIs group in Ukraine for 2000–2024 in 6-year increments (as of 01.10.2024)

Thus, the number of registered TNs of fluoxetine decreased over 24 years from 7 in 2000 to 4 in 2024; citalopram was not registered in 2000, the number of its TNs was relatively stable and decreased to 1 LP in 2024; paroxetine demonstrated constancy in the number of TNs throughout the analysis, which in 2024 amounted to 7 LPs; sertraline TNs were the largest in 2012 13), and in 2024 their number decreased to 9; fluvoxamine was characterized by relative stability of TNs over the specified period (2–3); escitalopram demonstrated the greatest increase in TNs – from the absence in 2000 to 22 TNs as of 01.10.2024, which indicates the greatest prospects for the development of the market of this particular INN from the SSRIs group [4].

It was found that at the end of the study, the majority of registered TNs of all 6 INNs of SSRIs had an unlimited shelf life (68.9 %) and were also of foreign origin (80.0 %).

Subsequently, based on the results of processing data from the State Register of Medicines of Ukraine as of October 1, 2024, the studied TNs of **group N06AB "Selective serotonin reuptake inhibitors"** were distributed by country of origin, domestic manufacturing companies, pharmaceutical form, and dosage (Fig. 3–6).

As the analysis data presented in Fig. 3 indicate, the TN under INN **N06AB03 Fluoxetine** is equally represented (50 %) by imported and domestic drugs, which are produced by PJSC "Kyivmedpreparat" and LLC "Corporation "Zdorovya". Both imported drugs come from India. All TN under this INN are presented in one dosage – 20 mg per 1 solid DF, among which capsules prevail (75 %).

Currently, in the State Register of INN **N06AB04 Citalopram** is presented in the form of 1 TN in LF tablets of 20 mg produced in Denmark.

Only one dosage (20 mg) in the form of tablets is characteristic of INN **N06AB05 Paroxetine**, and the distribution of its TN by origin is presented in Fig. 4.

As the results of the analysis (Fig. 4) indicate, among the 7 TNs of paroxetine, only 1 domestic drug (14 %), which is produced by LLC "Pharma Start", is imported, one each from Cyprus, Spain, India, Portugal, Hungary and Poland (16.66 %).

Fig. 5 shows the assortment analysis of TN **N06AB06 Sertraline**. Thus, among the 9 TNs of sertraline, 1 TN (11 %) is also a drug of domestic origin, which was registered by LLC "Corporation "Zdorovya", and 8 others – 1 TN (12.5 %) each come from 8 countries.

If INN N06AB03 Fluoxetin, N06AB04 Citalopram, N06AB05 Paroxetin are used in one dosage (20 mg), then the following 3 INNs have dosage variations. So, the drug Sertraline is produced in dosages of 25, 50, 100 mg, among which 50 mg per 1 DF prevails (53 %). Among all 17 drugs of this INN (considering dosage), only 1 registered drug is manufactured in the form of capsules (Zaloks, Canada), all the others are tablets (94 %).

Drug **N06AB08 Fluvoxamine** is represented by 2 imported TNs from Germany and France in one DF tablets in two dosages – 50 and 100 mg.

Fig. 6 shows the result of the study of the assortment analysis of the registered TN **N06AB10 Escitalopram**.

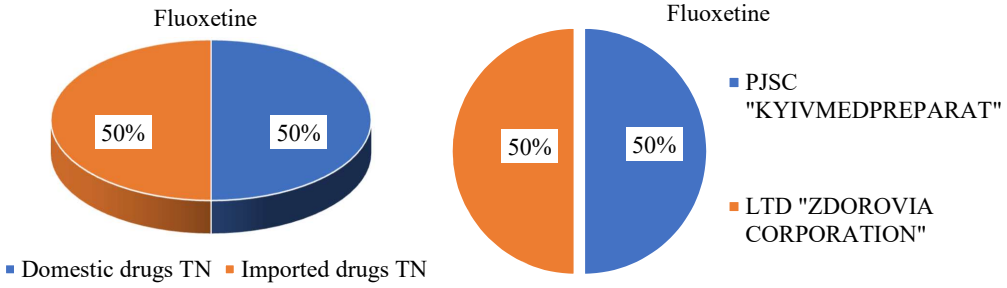

Fig. 3. Distribution of all registered fluoxetine TNs in Ukraine by origin and domestic TNs by manufacturing companies (as of 01.10.2024)

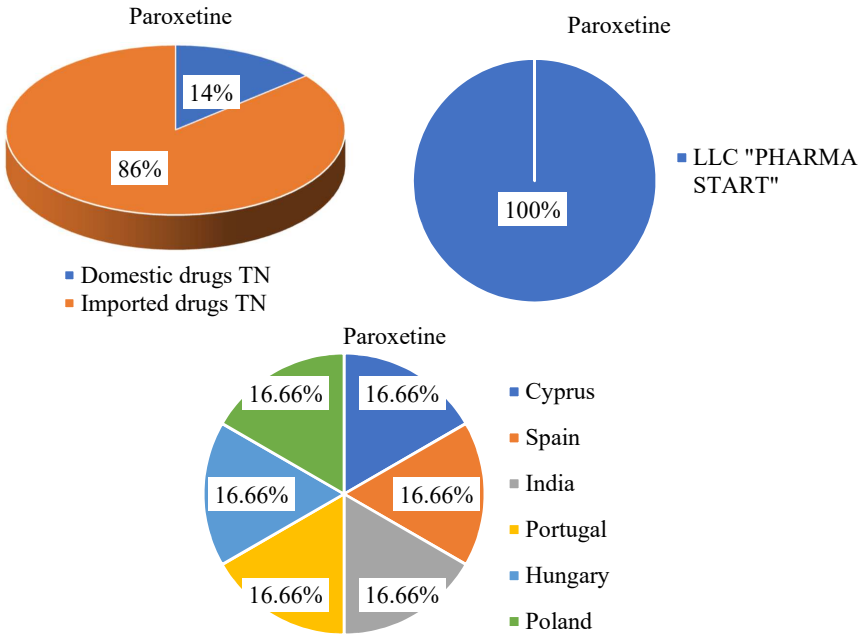

Fig. 4. Distribution of all registered in Ukraine TN of paroxetine by origin and importing countries (as of 01.10.2024)

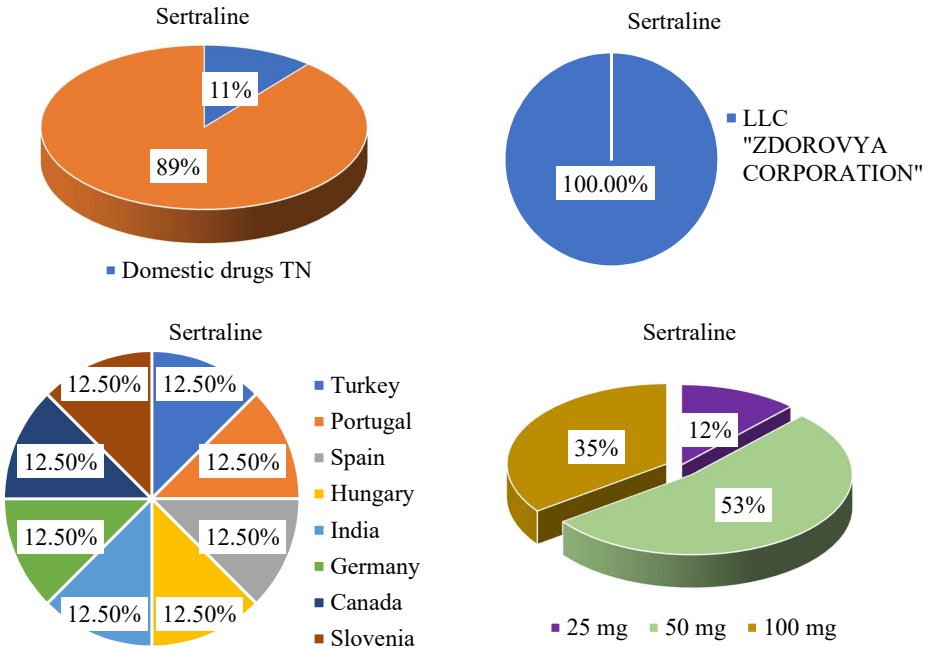

Fig. 5. Distribution of all registered sertraline TNs in Ukraine by origin, importing countries, domestic TNs by manufacturer and dosage in total (as of 01.10.2024)

Thus, among the registered TNs of escitalopram, imported drugs prevail, the share of which is 77 %. Among the 10 importing countries, the largest number of TNs is represented by India (35 %), Slovenia and Greece (11.5 % each), the remaining 7 countries registered 1 TN each, which is 6 %. 5 domestic TNs are produced at 4 manufacturing plants: LLC "Pharma Start" (40 %), LLC "Kharkiv Pharmaceutical Enterprise "Zdorovya Narodu", JSC "Kyiv Vitamin Plant", LLC "NVF "Mikrohim" (20 % each). Among the 22 TNs of escitalopram, 21 (95 %) TNs are registered in DF tablets in dosages of 5, 10, 15, 20 mg. All TNs in tablet form have a dosage of 10 mg (100 %), the majority, in addition to it, also have a dosage of 20 mg (90 %); additionally, 38 % of TNs submitted a dosage of 5 mg for registration, and 10 % submitted a dosage of 15 mg. In general, the dosage range is as follows: 10 mg (45 %)→20 mg (40 %)→5 mg (11 %)→15 mg (4 %) (Fig. 6). 1 TN is registered in the DF as oral drops, solution, 20 mg/ml, 15 ml in a dark glass bottle with a dropper stopper and a child-resistant cap.

At the next stage of the marketing analysis, the presence of the TN group **N06AB "Selective serotonin reuptake inhibitors"** in the Ukrainian pharmaceutical market was studied. The study of the pharmaceutical market wholesale segment was conducted according to Proxima Apteka data [24], posted in the software and information complex "APTEKA Weekly" – Apteka.UA

on the Morion publishing house portal [16]. Data processing took place in the first decade of October 2024. At that time, data as of 08/30/2024 were available.

Thus, the Proxima Apteka service [24] offered a price of 3 TN (75 %) out of 4 TNs of fluoxetine; 1 TN of citalopram (100 %) out of 7 TNs of paroxetine; 7 TNs of sertraline (78 %) out of 9 TNs of fluvoxamine (2 TNs of fluvoxamine); 15 TNs of 22 TNs of escitalopram (68.18 %). Thus, it was established that the 6 registered INNs of group N06AB "Selective serotonin reuptake inhibitors" together represented 45 TNs, of which 34 TNs were present on the wholesale market, which amounted to 75.56 %.

Among wholesale warehouses (bases), offers from BaDM (branch), Optima-Pharm (branch), LAKS (Nizhyn), O.L.KAR. Farm-Service (Shargorod), Ametrin (Kharkiv), Volynfarm (Lutsk), Koneks (Vinnytsia), etc. dominated.

The analysis of the **retail** segment of the domestic pharmaceutical market was conducted according to data from Apteka.UA [16] and Tabletky.UA [17]. It was found that the retail market offered a total of 37 TN (82.22 %), i.e. 3 TN more, compared to the wholesale market. Considering the dosage and number of units in the package of LF, the price analysis covered 52 drugs. A comparative analysis of both mentioned online drug booking services was conducted at the lower limit of retail prices in Kyiv.

Thus, it was established that the lower limit of retail prices in 27 drugs (51.92 %) was lower by a total of 8.11 % on Tabletky.UA compared to Apteka.UA; in 10 drugs (19.23 %) the lower limits of retail prices were the same; in 5 drugs (9.62 %) the retail price on Tabletky.UA was 8.02 % higher than on Apteka.UA; another 8 drugs (15.38 %) were absent on both platforms; and 1 TN in 2 DFs (3.85 %) was offered only by Apteka.UA. Since in 51.92 % of cases the Tabletky.UA service was more accessible to the consumer, further price analysis of the retail segment of the DF was carried out according to the data of this source. It was also calculated that on Tabletky.UA, the retail price of one half of the studied TNs was lower on average by 28.18 % than on the wholesale market according to Proxima Apteka, and for the other half, it was higher on average by 9 %.

Further, a comparative analysis of the retail price of those dosages and forms of release of the studied INNs, which represent the widest range of manufacturers, and which are most often used by patients, is presented. Thus, Fig. 7 shows the comparative retail price of a unit of DF fluoxetine 20 mg of 4 manufacturers in 6 drugs as of the first decade of October 2024.

So, the retail price of 20 mg of this INN ranged from 2.05 to 4.36 UAH, and the most affordable for patients was domestic Fluoxetine, tab. p/o 20 mg No. 20 (Zdorovya Corporation) at a retail price of 2.05 UAH per 1 tablet. As can be seen from the diagram, domestic analogues of fluoxetine were more affordable. Their cohort also includes the drug Flutisal, manufactured by the Indian company "Kusum Healthcare PVT" by order of LLC "Gledpharm LTD", Ukraine.

Citalopram is presented on the retail pharmaceutical market in the form of 1 drug (Cipramil, tab. v/o 20 mg No. 28, H. Lundbeck A/S, Denmark) at a retail price of 34.74 UAH per 1 tablet of 20 mg (Fig. 8).

The retail market for fluvoxamine, like citalopram, was not diverse, since this drug was registered and offered in Ukraine by only 2 foreign manufacturers: STADA, Germany and Mylan Laborat. SAS, France at a retail price for 1 tablet of 100 mg – 20.29 UAH and 40.75 UAH, respectively (Fig. 8). The range of retail prices for INN N06AB05 Paroxetine is presented in Fig. 9.

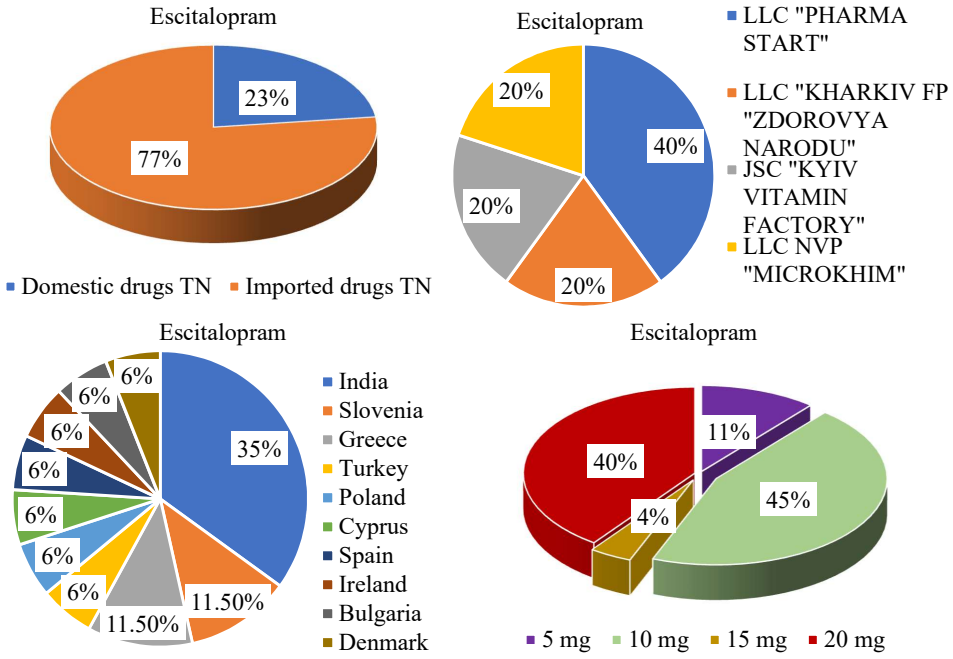

Fig. 6. Distribution of all registered TNs of escitalopram in Ukraine by origin, importing countries, domestic TNs by manufacturing companies and dosage in total (as of 01.10.2024)

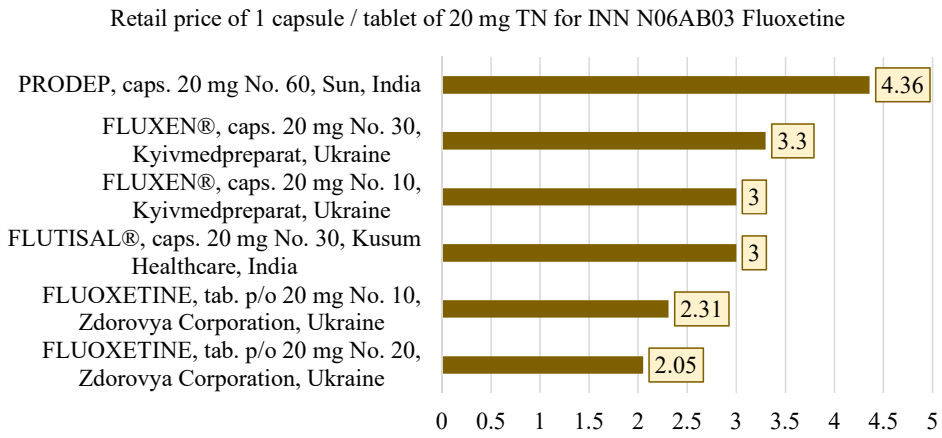

Fig. 7. Comparative analysis of retail prices of a unit of DF INN N06AB03 Fluoxetine from different manufacturers (as of 10/10/2024 in Kyiv), UAH

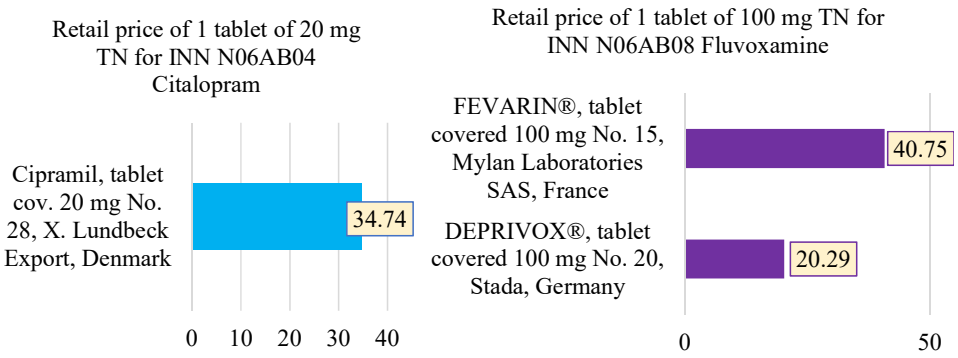

Fig. 8. Comparative analysis of retail prices of a unit of DF INN N06AB04 Citalopram (left) and INN N06AB08 Fluvoxamine (right)

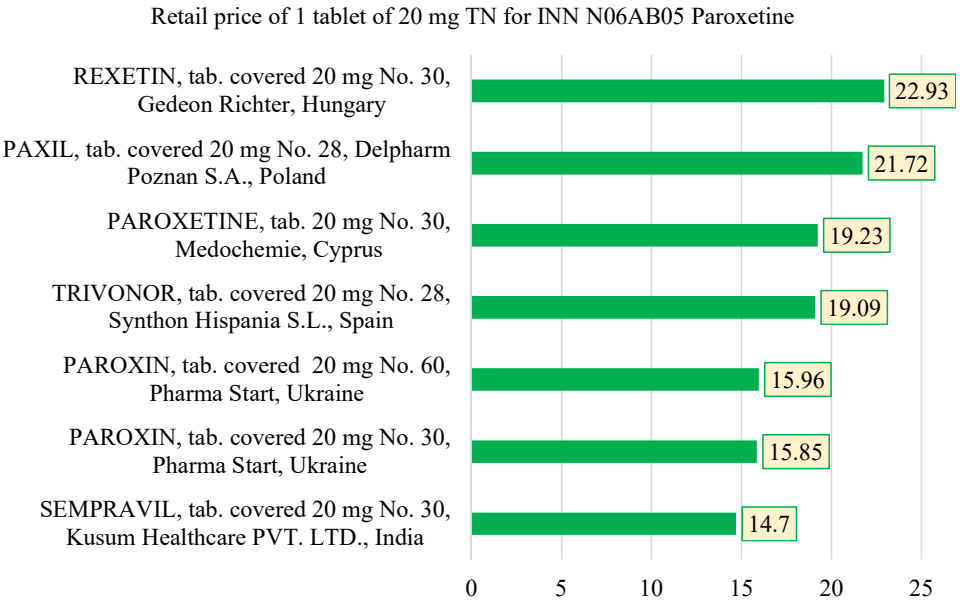

Fig. 9. Comparative analysis of retail prices of a unit of DF INN N06AB05 Paroxetine from different manufacturers (as of 10.10.2024 in Kyiv), UAH

The results showed that the retail price of 1 tablet of paroxetine 20 mg was within 14.70–22.93 UAH (Fig. 9). These data should be considered when planning the course of treatment of patients with the consequences of PTSD, which, as a rule, lasts from 6 months [5]. The most affordable was Indian-made paroxetine, the most expensive was Hungarian. At the same time, the cheapest in terms of retail price of 20 mg of paroxetine, the Indian drug Sempravil (Kusum Healthcare PVT) was also manufactured by order of the domestic LLC "Gledpharm LTD". Another drug of this INN – Proxetin-Darnitsa, manufactured by the Portuguese Blupharma Industry for

the domestic PrJSC "Pharmaceutical Firm "Darnitsa", was absent in the wholesale and retail segments of the pharmaceutical market.

In Fig. 10 graphically presents the gradation of the lowest retail price of a unit of sertraline 50 mg depending on the drug manufacturers.

Thus, the lowest was the retail price of 50 mg sertraline tablets in the drug Sertralin-Darnitsa, manufactured by the Spanish company "Farmex Advanset" for the Ukrainian "PC Darnitsa", the highest was Zoloft (Germany, "Pfizer"). The ratio between the price ranges was 1:6. The widest choice among drugs of the N06AB SSRIs group has the INN N06AB10 Escitalopram (Fig. 11).

As the results of the price analysis of escitalopram TN shown in Fig. 11 show, out of 22 registered TNs in the dosage of 10 mg, which is most often prescribed by doctors, the retail market offers 16 (73 %). In addition, one TN is presented in 2 quantities per package. Therefore, a comparison of the retail price was carried out between 17 drugs. It revealed that the price of the cheapest TN (Cyclox®, tab. covered 10 mg No. 56, Kusum Healthcare PVT LTD, India) and the most expensive original TN (Cipralex, tab. v/o 10 mg No. 28, H. Lundbeck A/S, Denmark) differs by 9.56 times, which indicates the social orientation of the retail market of this INN and creates ample opportunity for manoeuvres for both the doctor and the first-contact pharmacist.

At the next stage, a study was conducted of the presence of registered drugs of the N06AB group "Selective serotonin reuptake inhibitors" in SERLD in Ukraine (Tables 2–6), namely:

1 – National list of EMLs subject to state price regulation [18];

2 – State Drug Formulary (SDF): sixteenth issue [19];

3 – Register of wholesale prices (WPP) for medicinal products with declared changes, updated on 09/26/2024;

4 – The list of drugs subject to reimbursement under the program of state guarantees of medical care for the population, as of August 23, 2024, approved by order of the Ministry of Health No. 1537 dated September 4, 2024 [21].

Analysis of the presence of the drug N06AB03 "Fluoxetinum" in SERLD revealed that 3 out of 4 registered fluoxetine drugs are present in all SERLDs. Fluoxetine, which was the only EML, became the first INN from SSRIs, which in 2021, together with 56 TNs for the treatment of mental and behavioural disorders, epilepsy (INN – amitriptyline, valproic acid, haloperidol, carbamazepine, clozapine, lamotrigine, risperidone), was included in the Register of Drugs, the cost of which is subject to reimbursement [25]. When writing a prescription for a patient for the drug Fluoxetine, tab. 20 mg No. 20, Zdorovya – treatment with this drug will be free of charge, and the pharmacy will be fully reimbursed by the state. The other 2 drugs (Fluxen, KMP and Flutisal, Kusum Healthcare) will require co-payment – from the patient and the state.

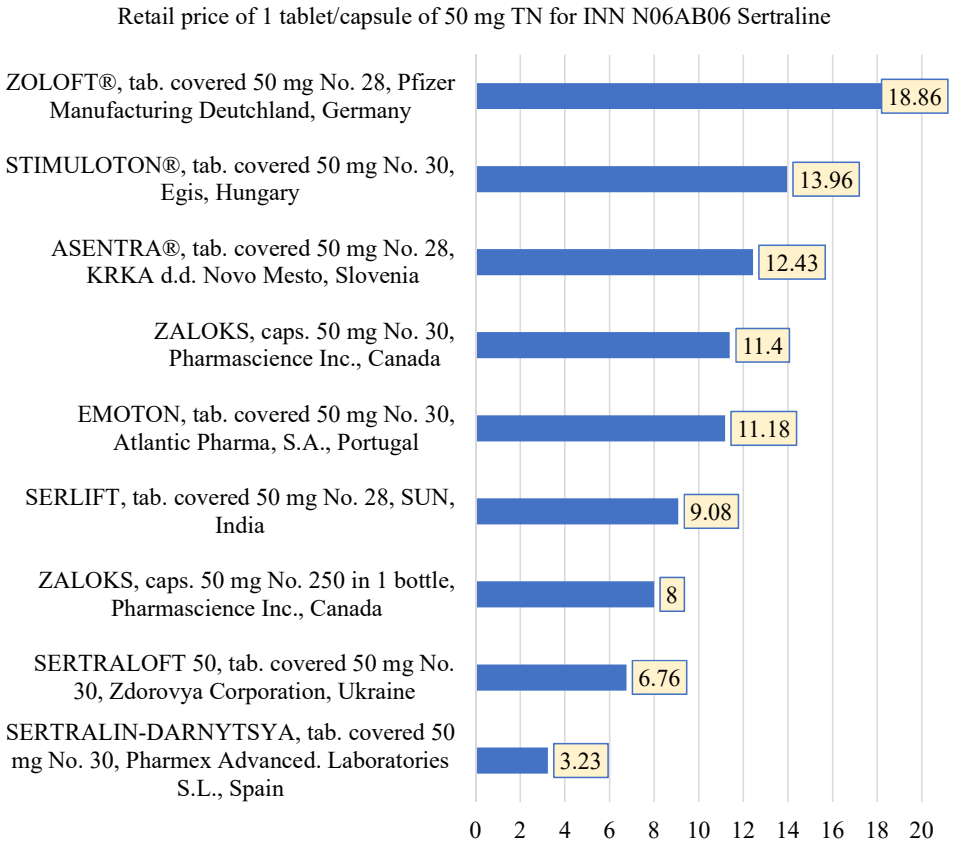

Fig. 10. Comparative analysis of retail prices of a unit of DF INN N06AB06 Sertraline from different manufacturers (as of 10.10.2024 in Kyiv), UAH

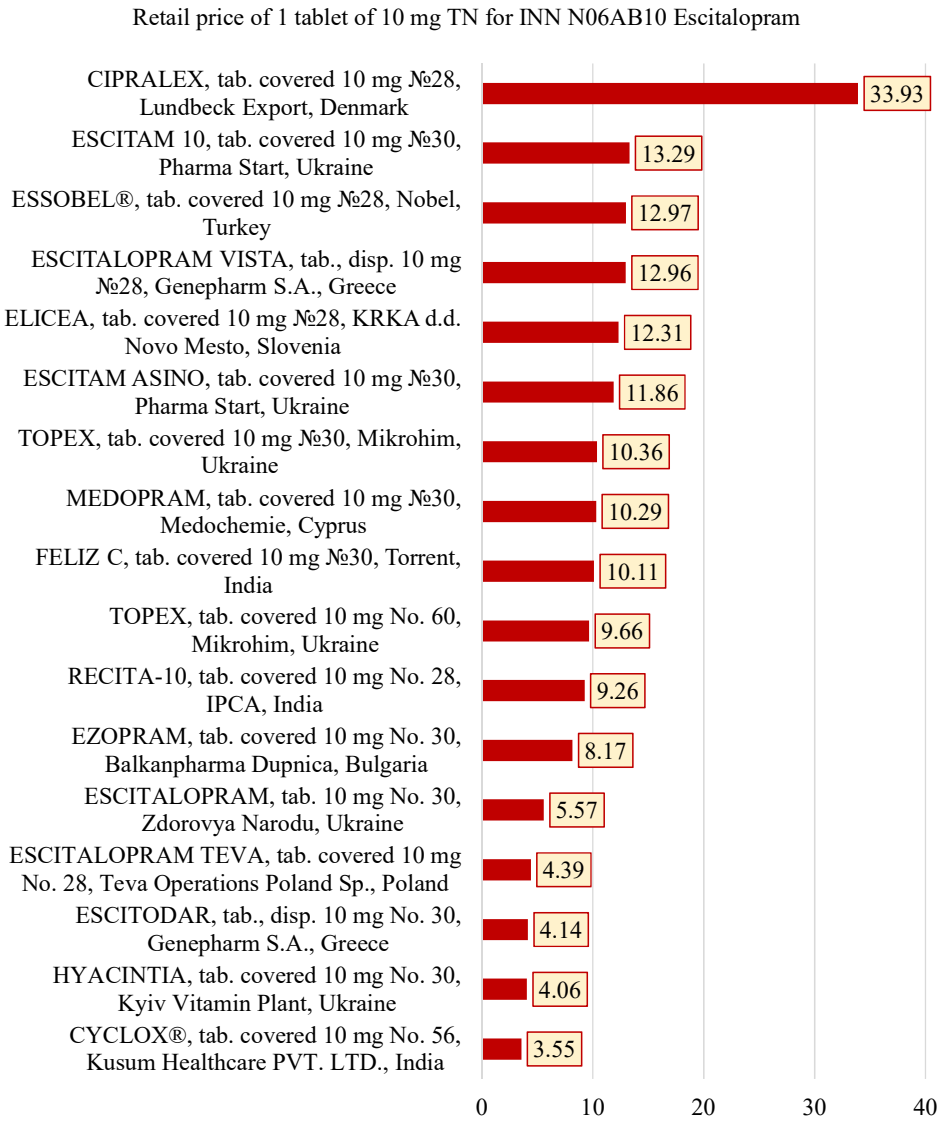

Fig. 11. Comparative analysis of retail prices of a unit of DF INN N06AB10 Escitalopram from different manufacturers (as of 10.10.2024 in Kyiv), UAH

The only drug product of citalopram (Cipramil, Lundbeck A/S) and 2 registered drugs of fluvoxamine (Deprivox®, Stada and Fevarin, Mylan Lab.) from 4 SERLDs are present only in the SDF – their cost for domestic patients is not reimbursed.

In contrast, all registered TNs of paroxetine are included in the National List of EML, are present in the 16th issue of the SDF (except for the one absent from the FR Proxetin-Darnytsia, Blupharma) [19], and Sempravil, tab. 20 mg No. 30, Kusum Healthcare for patients may be free of charge according to the order of the Ministry of Health of Ukraine No. 1537 [21].

Registered medicinal products of paroxetine, as well as sertraline and escitalopram, which were present in the SDF, were first included in the National List of EML by the Resolution of the Cabinet of Ministers of Ukraine dated 21.06.2024 No. 733 "On Amendments to the Resolution of the Cabinet of Ministers of Ukraine dated 25.03.2009 No. 333" [26], and then - in the reimbursement list by the Order of the Ministry of Health of Ukraine No. 1537 dated 04.09.2024, which entered into force on 30.09.2024 [21]. Among the TN of sertraline, only Sertraline-Darnytsia, Farmex Advanset are reimbursed and then without co-payment from the patient. Since the study was conducted immediately after the change in the status of SSRIs, some inconsistencies were found in the SERLD. Thus, Sertraline-Darnitsa, Farmex Advancet, which is the only sertraline fully reimbursed by the state, is not included in either the SDF or the Register of WPP.

At the same time, among the 5 TN escitaloprams that are subject to reimbursement, none was included in the Register of WPP, and the drug Escitodar, Jenepharm was absent from both the SDF and the database "National List of EMLs for which state price regulation is established".

As indicated by the SERLD analysis result, among the escitalopram drugs, Cyclox, Kusum Healthcare in both recommended dosages (10 and 20 mg) No. 56 and Hyacinthia, KVZ in a dose of 20 mg No. 30 will be completely free of charge for the patient. Partial payment is provided for the 3 other reimbursed escitalopram drugs.

5. Discussion of research results

Analysis of literature sources and an anonymous survey of doctors revealed that drugs of the N06AB group "Selective serotonin reuptake inhibitors" should be considered as first-line pharmacotherapy for military personnel with PTSD. The updated Unified Clinical Protocol for Primary and Specialized Medical Care "Acute Stress Reaction. PTSD. Adaptation Disorders", approved on 07/19/2024, recommends using paroxetine, sertraline, and fluoxetine with SSRIs for drug intervention [5]. Regarding paroxetine and sertraline as pharmacotherapy for military personnel with PTSD, this recommendation coincides with the practical recommendations of the US Departments of Veterans Affairs and Defense (VA/DoD) [6, 7], the use of fluoxetine is recommended by the WHO List of Essential Medicines [9], and all three drugs: paroxetine, sertraline, and fluoxetine are recommended by M. Hoskins et al. [8].

At the same time, according to the results of studies by O. Mishchenko and N. Bezditko [10], who processed these meta-analyses, patients with PTSD had the most pronounced clinical effect when treated with escitalopram, compared to other SSRIs, namely: a positive effect on the state of microglia and neuroinflammation induced by it, a decrease in inflammatory markers, which provides its multi-vector mechanism of action; combines the properties of an antidepressant and a neuroprotector. These authors, having analyzed the results of the analysis of 10 studies involving 2687 patients, stated that escitalopram had a significantly higher overall effect of therapy, the degree of response and remission compared to all comparators, including paroxetine and sertraline. Escitalopram also held the leading ranks in the rating of effectiveness and tolerability among 21 antidepressants in a network meta-analysis of 522 trials involving 116,477 patients [10]. Therefore, escitalopram is the leader in pharmacy sales and positive registration dynamics in Ukraine in recent years [13, 14].

However, escitalopram, the market of which in Ukraine shows the greatest growth in terms of assortment and which is the most numerous included in the List of Medicines Subject to Reimbursement under the State Health Care Guarantees Program, remains absent from the Unified Clinical Protocol. In addition, it is advisable to bring its representatives into compliance with regulatory requirements in the current socio-economic lists of medicines in Ukraine, namely: to include all its representatives, primarily those subject to state reimbursement, in the State Formulary of Medicines and the Register of Medicines and Medical Devices for which wholesale prices have been declared [19, 20].

In addition, using the example of a separate ATC group of drugs, certain current trends in the pharmaceutical market can be outlined, namely: a significant presence of drugs manufactured by foreign manufacturing companies, the applicants of which are domestic manufacturing plants. Moreover, the prices of such drugs are close to the prices of the cheapest domestic analogues. In addition, it was established that currently the lowest prices for drugs in Ukraine are offered by the Tabletky.UA service, where the retail price of drugs is lower than the wholesale offers on Proxima Apteka. It was also established that the state reimburses the cost of treatment with the most affordable drugs, namely: among fluoxetine analogues, the cheapest and at the same time reimbursed drug was Fluoxetine, Zdorovya, Ukraine; among paroxetine drugs – Sempravil, Kusum Healthcare, India; sertraline – Sertraline-Darnitsa, Farmex Advanced Laboratories, Spain; Escitalopram – Cyclox, Kusum Healthcare, India. These drugs are completely free for patients under the government program "Affordable Medicines", and citalopram and fluvoxamine drugs were not included in this program. At the same time, Indian and Spanish manufacturers manufactured their drugs to order from domestic companies: LLC "Gledpharm LTD" and PrJSC "FF "Darnitsa", respectively.

Practical significance. The results of this study can be used by psychiatrists and general practitioners of family medicine in the process of prescribing prescriptions to military personnel and war veterans with PTSD when choosing those drugs that are subject to reimbursement, which will promote adherence to treatment, since currently in Ukraine, PTSD treatment with these drugs can be free of charge or with a minimal co-payment for the patient. The results of the study will also be useful for pharmacy employees when forming an order, given the great need for SSRIs during the Russian-Ukrainian war and afterwards – during the overcoming of its consequences.

In addition, the results of the study revealed a regulatory and legal inconsistency in the presence of SSRIs in the socio-economic lists of medicines, which should be eliminated in the near future.

Study limitations. Research into the pharmaceutical market and legal status of SSRIs was limited to Ukraine.

Prospects for further research. Considering that escitalopram has the highest indicators of efficacy, safety [10], as well as the number of registered drugs, market presence and the highest number of representatives subject to reimbursement, it is advisable to recommend its inclusion in the Unified Clinical Protocol of Primary and Specialized Medical Care "Acute Stress Reaction. Post-Traumatic Stress Disorder. Adaptation Disorder". In addition, the authors are developing a Pharmacist Protocol "Dispensing of Medicines. Promoting Adherence to Treatment in Post-Traumatic Stress Disorder".

6. Conclusions

1. An anonymous survey of 35 psychiatrists and 25 neurologists was conducted to determine the frequency of their prescription of antidepressants and their representatives to patients with PTSD. Thus, 100 % of doctors confirmed the choice of SSRIs among subgroups N06A "Antidepressants". From the subgroup N06AB SSRIs by INN, psychiatrists most often prescribed escitalopram and sertraline, neurologists – citalopram, which is a racemic mixture of R-(-)-citalopram and S-(+)-citalopram, and escitalopram, and respondents in general – escitalopram. With a probability of error of the first type $\alpha=0.05$, a reliable probability of $p\geq0.95$, the respondents' answers to the questionnaire questions were unanimous.

2. An analysis of the dynamics of registration of SSRI drugs in Ukraine revealed that over the past 24 years, escitalopram was characterized by the greatest increase in the number of trade names: +22 drugs, and over the past 6 years+14, which indirectly indicates better indicators of the drug's effectiveness and safety, to which the pharmaceutical market responded with a sharp increase in offers.

3. The distribution of registered finished medicines of the N06AB group by country of origin, domestic manufacturing companies, and dosage form stated that as of 01.10.2024, 45 trade names of the group were registered in Ukraine (4 – fluoxetine, 1 – citalopram, 7 – paroxetine, 9 – sertraline, 2 – fluvoxamine, 22 – escitalopram), 68.9 % of which had an unlimited shelf life; 80 % of medicines were of foreign origin, 20 % of which were manufactured to order by domestic manufacturing companies, which were applicants for the registration of medicines in Ukraine. Imported medicines came from 15 countries, most of all from India (28 %), Spain and Slovenia (8 % each), the remaining countries represented 1-2 medicines each; among the 9 domestic companies, the largest number of products is produced by LLC "Pharma Start" (33 %) and Pharmaceutical Company "Zdorovya" (22 %); 100 % of the drugs are for oral use, produced in the form of tablets – 89 %, capsules – 9 %, oral solution – 2 %.

4. A study of the state of the SSRIs pharmaceutical market showed that the degree of presence of drugs in the wholesale segment was 75.56 %, in the retail segment – 82.22 %. It was established that the resource for searching and booking drugs Tabletky.UA, according to the lower limit of retail prices in Kyiv, offered 50 % of the studied drugs at a price lower than in the wholesale market, and the other 50 % – with an average retail markup of 9 %; also, in 51.92 % of trade names on this service, the retail price was on average 8.11 % lower, compared to Apteka.UA, in another 19.23 % of drugs, the lower limits of retail prices were the same.

5. A price analysis was conducted by comparing the retail cost of a unit of dosage form of different trade names and comparing its results with the analysis of the List of Reimbursable Medicinal Products, which revealed that currently the state reimburses the cost of treatment with the most affordable drugs paroxetine and sertraline (1 trade name each), fluoxetine (3 preparations), escitalopram (5 drugs), which again indicates the greatest trust in this representative of the group. Therefore, given the results of the marketing research, it is recommended to include it in the Unified Clinical Protocol for the treatment of patients with PTSD.

Conflict of interests

The authors declare that they have no conflict of interest regarding this study, including financial, personal, authorship, or other, that could influence the study and its results presented in this article.

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Data availability

Data will be available upon reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies in the creation of the current work.

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