The Current Market of Pharmacological Drugs for the Prevention and Treatment of Obesity in Ukraine: A Review

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ABSTRACT

Obesity is one of the problems of current century, which is the cause of complex disorders of organs and systems of the human body, up to the development of lethal outcomes. The modern market of pharmaceutical medicine preparations for treatment and prevention is quite extensive. The main treatment of diseases that is proven on the basis of evidence, including for preventive purposes, is the inclusion of such drugs in fever protocols throughout the country. The purpose of this study is to examine the current market of drugs for the prevention and treatment of obesity in Ukraine.

Introduction

According to the modern interpretation, obesity (adipositas) is a deposit of fat in the body that exceeds its norm in healthy people. As noted in the Pharmaceutical Encyclopedia, obesity, as a separate nosological unit, includes all cases when excess fat is not a consequence of a disease, but a major pathological disorder with an unidentified primary lesion of any organ or organ system. Modern medical practice treats and considers obesity as a chronic disease that requires a set of treatment and prevention measures to correct body weight through a balanced diet, increase physical activity, use of specific drugs, and in the absence of such measures – surgery. It is known that the success of the therapeutic process depends not only on the general health of the patient, prevention, on quality of medication, compliance between doctor and patient, but also on the form and method of administration, depending on individual characteristics of the patient. This requires drug analysis and careful selection of patient management tactics in order to improve the quality and increase the patient's life expectancy. The causes of the development, prevalence, prevention and treatment of obesity, including with the help of drugs, is the subject of analysis of many scientific and experimental studies (Mohamadi Yalsuyi et al., 2022; Mohammed et al., 2021; Raheem et al., 2022). In particular, in the publications of Zhuravlyova and Rogachova (2017), Prymachenko (2018), Vasendin (2015), Smetanina (2006, 2016), Endalifer and Diress (2020) and others the reasons and conditions of development of such pathology are considered.

Methods
The research materials published data from various sources of information on the availability of drugs and methods of treatment of obese patients and used the analytical search method of modern information systems. We conducted an analysis of the modern market of drugs for the treatment and prevention of obesity. The objects of the study were search databases of evidence-based medicine, the website of the Ministry of Health of Ukraine and others. Information about the real state of registration and a certain level of evidence of therapeutic effectiveness, pharmacological safety of drugs for the treatment and prevention of obesity was of particular interest. The basis of modern evidence-based medicine is the Cochrane collaboration; PubMed database (MEDLINE); database of abstracts of effects (DARE); Medscape. An analysis of the State Register of Medicinal Products of Ukraine was also conducted.

Results and Discussion
The analysis showed that in the 1930s, laxatives were actively used for weight loss: Medilax (Purgen) (the active substance is Phenolphthalein). As stated in the publication of Andriychuk, Smetanina et al. (2022), the implementation and use of Purgen is currently suspended and prohibited. In the 1950s, Ethylamphetamine (Adiparthalop, Apetinil, Ethamphetamine) was preferred in the treatment of obesity. It is currently not approved for use in the US, EU due to confirmed extreme toxicity (Bluher 2019, Garvey et al., 2014). On the pages of Evidence-based Medicine Sites, information is provided that in the 1970s, drugs included in the group "A08 Drugs for the treatment of obesity (except dietary products)" and those with separate ATC codes were used to treat obesity: Katyn (Alvalin, Anti-adiposit X112T, ReliSlim) - prohibited in the EU, USA, CIS countries; Clobenzorex (Asenlix, Dinintel, Finedal, Itravel, Obeclox, Rexigen) - prohibited in the EU, USA, CIS countries, permitted for use in Mexico and Latin America; Mefenorex (Pondinil, Rondimen) is prohibited in the EU, the USA, the CIS countries due to a large number of side effects up to the development of a fatal outcome. The publication of Klymyshina and Smetanina (2018) and Andriychuk et al. (2021) also considers these issues. In the protocols of the pharmacist (2014), it is noted that modern drugs for the treatment of obesity belong to groups A08AA (drugs of central action), A08AB (peripheral action), and A08AH (others) according to the ATS classification (Table 1). According to Safaei et al., 2021, Smetanina (2009), and other, there are many other groups, but they are mainly auxiliary or supportive therapy. It is worth noting that most drugs intended for the prevention and treatment of various stages of obesity show the effect of tolerance and the possible development of dependence on them. In addition, almost all drugs for weight loss, except for Xenical, are included in the list of "regulated substances". Slimming drugs have side effects, most of which are minor (some may be unpleasant) and usually disappear over time as the body adapts to pharmacotherapy. In some cases, serious complications with the development of fatal outcome are possible. There are restrictions on the use of all weight loss drugs, especially for the elderly and children. Therefore, the use of such drugs is controlled, prescribed by a doctor and self-medication without consulting a family doctor is prohibited.

Ukraine has a legally approved EU integration strategy, which provides for measures to harmonize the regulatory framework, in particular the system of standardization and certification of medicines in Ukraine, with EU standards and directives. In the pharmaceutical industry, such harmonization makes it possible to increase the level of quality assurance of drugs, to unify requirements for registration and licensing. The main requirements for drugs are quality, efficiency, safety. This fact is shown in the publications of the author of this post in different years (Smetanina 2010, 2019). All medicinal products (drugs) in circulation in Ukraine must meet the requirements of global quality indicators: Pharmaceutical Development, Standards of Good Practice (GLP, GCP, GRP, GMP, GSP, GDP, and GPP), Good Practices of the pharmacological supervision of safety and efficacy. Recently, a medical approach to the tactics of managing patients, built on the principles of evidence-based medicine, has become widespread. The Pharmaceutical Encyclopedia and the pages of the Pharmaceutical Wikipedia call EBM medicine that is based on available evidence of the effectiveness and safety of drugs that have undergone a pharmacoepidemiological study using mathematical estimates of the probability of success and risk. A number of authors emphasize this in their publications: Finer et al., 2000, Ball et al., 2009, Hung et al., 2015, Bauer et al., 2020 and others. The analysis of published experiments on the internet are presented
in Table 2. We conducted an analysis of sources of evidence, which revealed that for the treatment and prevention of obesity at the present stage, the following drugs are used:

- Orlistat (Xenical, Alli): Proven effectiveness of the drug in weight loss by 2% more than placebo in the period from 4 to 24 months of use. In 2010, the Food and Drug Administration (FDA) conducted a safety review of Orlistat for reports of liver dysfunction in a small number of people taking it. In order to prevent disorders that may indicate liver damage, it is recommended to use Xenical or Alli as a substitute for Orlistat. Available over-the-counter in small doses in the United States. Not registered in Ukraine.

- Lorcaserin (Belvik): It is a drug for complex therapy, blocks the urge to starve, allowing patients to feel full with minimal food intake. Registered in the United States in 2012. Recommended by the FDA for long-term use. Belvik was rejected by the FDA at the beginning of the implementation (fears were based on the fact that its principle is similar to Fenfluramine - which was withdrawn from the market due to adverse effects on heart valves), but later manufacturers provided additional research data permission to sell. There is no reliable evidence that Belvik worsens the condition of the heart valve. The FDA requires manufacturers to develop medical strategies for risk assessment and response strategies (REMS). Prescription drug (USA). Subject to control under the Controlled Substances Act. Federal law prohibits unauthorized sale or transfer to third parties. There is no registration in Russia. Not registered in Ukraine.

- Phentermine (Adipex): It is a drug of short-term use (not more than 12 months). The pharmacological action of the drug is the release of norepinephrine, which suppresses appetite. According to the All-Ukrainian Gastroenterological Organization (UGO) it is established that the use of Phentermine increases the patient's weight loss by 3-4% compared with placebo. Proven risk of Phentermine dependence (classified by the Drug Enforcement Agency, USA, as a controlled substance under Scheme IV). FDA-approved Phentermine brands: Adipex-P, Oby-Cap, Suprenza, T-Diet, Zantryl. In the United States, it is a prescription drug. It’s circulation is regulated by the Federal Controlled Substances Act. It is not allowed to be used in many European countries. Included in the “List of narcotic drugs, psychotropic substances and their precursors subject to control.” Subject to subject-quantitative accounting in Russia. Not registered in Ukraine.

- Topiramate: It is an antiepileptic drug used in obesity in patients with bipolar disorder. The UGO has been studied for a long time. The following Topiramate brands are represented in the United States: Topamax, Topamax Sprinkle, Topiragen. In February 2012, the drug Qsymia (Xymia) with the complex active ingredient Phentermine + Topiramate was registered in the United States. Xymia increases the risk of birth defects in the fetus of the patient who took this drug. In this regard, the FDA requires manufacturers to develop risk assessment and response strategies. Xymia is a prescription drug for the United States. In Russia, there is no drug with the active substance Phentermine (single drug or complex drug). Prohibited for use since 2009. Since February 2013, Xymia has been denied registration by the European Medicines Agency due to the possibility of developing heart attack during treatment. The drug has been banned from use in the EU and Ukraine since 2013.

### Table 1. ATC classification of drugs for the treatment of obesity

<table>
<thead>
<tr>
<th>ATC code</th>
<th>The name of the drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>08AA01</td>
<td>Phentermine</td>
</tr>
<tr>
<td>A08AA02</td>
<td>Sibutramine (Fenfluramine, Linmex)</td>
</tr>
<tr>
<td>A08AA03</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>A08AA04</td>
<td>Dexfenfluramine</td>
</tr>
<tr>
<td>A08AA05</td>
<td>Mazindol</td>
</tr>
<tr>
<td>A08AA06</td>
<td>Ethylamphetamine</td>
</tr>
<tr>
<td>A08AA07</td>
<td>Katin</td>
</tr>
<tr>
<td>A08AA08</td>
<td>Clobenzorex</td>
</tr>
<tr>
<td>A08AA09</td>
<td>Mefenorex</td>
</tr>
<tr>
<td>A08AA10</td>
<td>Sibutramine</td>
</tr>
<tr>
<td>A08AA11</td>
<td>Lorcaserin</td>
</tr>
<tr>
<td>A08AA56</td>
<td>Ephedrine in combination with other drugs</td>
</tr>
<tr>
<td>A08AA62</td>
<td>Bupropion and naltrexone</td>
</tr>
<tr>
<td>A08AB01</td>
<td>Orlistat (Alai, Xenical, Xenistat, Orlikel, Orlip, Orlistat, Orsoten, Symmetry)</td>
</tr>
<tr>
<td>A08AX01</td>
<td>Rimonabant</td>
</tr>
</tbody>
</table>

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https://jbcpm.com/
Table 2. The main sources of evidence-based medicine (EBM)

<table>
<thead>
<tr>
<th>Source EBM</th>
<th>The main characteristic of the source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDSR</td>
<td>Cochrane Database of Systematic Reviews</td>
</tr>
<tr>
<td>DARE</td>
<td>Database Abstracts of Reviews of Effectiveness</td>
</tr>
<tr>
<td>CCTR</td>
<td>Cochrane Controlled Trials Register</td>
</tr>
<tr>
<td>CMR</td>
<td>Cochrane Methodology Register</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment Database</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service: Economic Evaluation Database</td>
</tr>
<tr>
<td>Medline (USA)</td>
<td>Medlars online. MEDLARS: Medical Literature Analysis and Retrieval System</td>
</tr>
<tr>
<td>DynaMed (USA)</td>
<td>Dynamic Medical Information Systems</td>
</tr>
<tr>
<td>IOM (USA)</td>
<td>Institute of Medicine National Academy of Sciences</td>
</tr>
<tr>
<td>BE</td>
<td>Best Evidence Electronic version of 2 printed editions: ACP Journal Club and Evidence-Based</td>
</tr>
<tr>
<td>ACP Journal Club</td>
<td></td>
</tr>
<tr>
<td>British Medical Journal</td>
<td></td>
</tr>
<tr>
<td>The New England Journal of Medicine</td>
<td></td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence</td>
<td></td>
</tr>
<tr>
<td>EBM (Great Britain)</td>
<td>Evidence Based Medicine</td>
</tr>
<tr>
<td>Annals of Internal Medicine</td>
<td></td>
</tr>
<tr>
<td>HINARI</td>
<td>Health Inter Network Access to Research Initiative</td>
</tr>
<tr>
<td>NMCD</td>
<td>Natural Medicines Comprehensive Database</td>
</tr>
<tr>
<td>IBIDS</td>
<td>International Bibliographic Information on Dietary Supplement</td>
</tr>
</tbody>
</table>

- Bupropion: It is an antidepressant. In combination with Naltrexone, Contrave (a psychotropic drug) used to treat obesity in patients with nicotine dependence. According to studies conducted by UGO, in the treatment of obesity Kontrave (400 mg per day) for a period of 6 to 12 months, weight loss averages 4.4 kg, compared with placebo. In terms of weight loss, Orlistat, Sibutramine and Amfepramon are the most important. Trade names (TN): Aplenzin, Budeprion SR, Buproban, Forfivo XL, Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban, Zyban Advantage Pack, Budeprion XL Available in the United States only by prescription. In Russia with the active substance bupropion registered Velbutrin. Registered in Ukraine
since 2016 under the name Velbutrin (registration certificate (r.c.) UA/3844/01/01).

- Liraglutide: It is a drug for the treatment of diabetes. In 2017, the drug received a new ATC code A10BJ02 and it entered the new subgroup "A10BJ Analogs of GPP-1 receptors". Approved by the FDA since 2014 as an injectable drug for the treatment of morbid obesity and complicated forms of obesity. Studies conducted by the UGO have found that daily use of 3 mg of Liraglutide can cause 5% weight loss in 16 weeks. TN: Saxenda (Novo Nordisk, Denmark) and Victoza. They differ in the dose of the active substance - Liraglutide: Saxenda - 3.0 mg, Victose - 1.8 mg. Prescription drug. It has been registered in Ukraine under the name Victoza since 2017 (r.c. UA/12124/01/01).

- Amphetamone (Diethylpropion, Diethylcatinone, Tenuate): It is a drug similar to amphetamine, it has anorectic properties (irritate the central nervous system, thus causing the release of norepinephrine, which affects appetite suppression). According to the UGO, daily single use of Diethylpropion at a dose of 75 mg increases the patient's weight loss by 3-4% compared with placebo. FDA approved for short-term use only - up to 12 weeks. Brands and generics of Amfepramon approved in the United States: Tepanil, Diethylpropion hydrochloride. In the United States - a prescription drug. The Controlled Substances Act regulates the circulation of the drug. In Russia, it belongs to the II list of narcotic drugs and psychotropic substances with restricted circulation and state control of circulation. Not allowed free sale. It is banned in the EU. Not registered in Ukraine.

- Sibutramine (Meridia): It is an inhibitor of the reversal of serotonin and norepinephrine, the only drug that physiologically neutralizes the root cause of fat deposits.

- increases energy expenditure and gives a feeling of satiety. According to the UGO, taking 1 capsule a day helps to lose 5% or more weight than placebo. Sibutramine was approved in 1997 as a drug for weight loss, but in 2010, its sale on the market was limited, as studies have shown an increased risk of serious heart complications, including of myocardial infarction and stroke. In the United States, Sibutramine is subject to control under the Controlled Substances Act. In late 2010, the Meridia brand was recalled at the request of the FDA. In Russia, drugs that contain Sibutramine as an active substance (Goldline, Lindaxa, Meridia, Slimia, Reduxin) are subject to subject-quantitative accounting. In 2011, it was banned in most EU countries. Not registered in Ukraine.

- Rimonabant (Zimulti): It is a selective blocker of the cannabinoid receptor CB1, normalizes energy metabolism. According to the UGO, taking Rimonabant causes a moderate weight loss of 5% or more during the year. It was approved in most EU countries, as well as in Mexico and Argentina until 2009. Not approved by the FDA due to a number of side effects (depression, anxiety, nausea, diarrhea, suicidal ideation and suicide). Brand names: Zimulti, Acomplia, Bethin, Monaslin, Remonabant, Riobant, Slimona, Rimoslin, Riomont. In Russia, the drug with the active substance Rimonabant (Zimulti) was approved for use until 2009. Not registered in Ukraine. The drug is in new stages of research. Requires a number of qualitative studies with a long period of dynamic monitoring after treatment.

- Fenfluramine (Pondimin): It increases the feeling of satiety due to increased levels of serotonin in the brain. In the late 1990s, it was discovered that even small doses of Fenfluramine, especially in combination with Phentermine, could cause pulmonary hypertension and heart valve disease. Therefore, in the United States, the Controlled Substances Act is included in the CIV list and its sale or federal law governs transfer to third parties. Not registered in Ukraine.

- Dexfenfluramine (Minifage, Redux): It is a dextrorotatory isomer of Fenfluramine. Molecular weight, pharmacological action, indications and contraindications are similar to Fenfluramine. Banned for use in the late 1990s.

- Mazindol: It increases the feeling of satiety. In the United States, Mazindol is subject to control under the Controlled Substances Act. The Mizaron brand (USA) was recalled in 1973. The Sanorex brand was recalled in 1980 at the request of the FDA. Teronak (Russia) - currently not allowed for use. In Russia, it belongs to the list of III narcotic drugs and psychotropic substances with restricted circulation and state control. In free sale at present since 2014 is not allowed to use.

- Fluoxetine: This drug is an antidepressant, the drug of choice in the treatment of obesity in depressed patients who require concomitant use of antidepressants and drugs to lose weight. According to the UGO, Fluoxetine is appropriate only in patients with: sleep apnea, nocturnal cravings, and bulimia. First registered in 1974. Approved for use by the FDA in 1977. Manufacturer Eli Lilly received marketing authorization only in December 1987. Released from patent protection in 2001. Currently, the drug is approved for use only in mentally ill patients, as it causes agitation and can provoke suicide. Brands in the USA: PROzac, PROzac Weekly, Rapiflux, Sarafem, Selfemra, PROzac Pulvules. In Russia, it is registered under the names: Apo-Fluoxetine, Deprex, Deprenon, Portal, Prodep, Prozac, Profuza, Floxet, Fluvax, Fluxonil, Fluxin, Fluxetine, Fluxetine HEXAL, Fluxetine Lanluxer, Fluoxetine, Fluoxetine hydrochloride, Framex. It has been registered in Ukraine as Fluxetine since 2017 (r.c. UA/8591/01/01) and Fluxen (r.c. UA/1084/01/01).

- Metformin: It is a hypoglycemic drug for the treatment of type 2 diabetes, especially in overweight patients. Studies conducted at the level of UGO have shown that Metformin is relevant in the treatment of patients with impaired glucose metabolism in the body. The dose of the drug is selected depending on the level of glucose and taking into account whether the patient receives insulin. The maintenance dose is 100-200 mg per day. Studies show a high probability of death from various causes. Metformin brands in the USA: Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet. In Russia, registered drugs with the active substance metformin: Bahomet, Glycon, Gluminor, Gilformin, Glucophage, Langerin, Metadene, Methospadin, Metformagama 500 (850, 1000), Metformin, Nova Met, NovoFormin, Siofor 500 (850, 1000) Formentin, Formin. In Ukraine it is represented since 2014 as: Metformin-Teva (r.c. UA/12382/01/01, UA/7769/01/01, UA/7795/01/02), Metformin...
Conclusions
We conducted an analysis and studied the main range of modern drugs, analyzed their evidence base, trade synonyms and the state of use in different countries. The study can be used to further develop modern drugs for weight loss with a wide therapeutic range, easy tolerability, and high efficiency and availability groups of overweight patients.

Declarations
Conflict of interest
There are no conflicts of interest.

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Consent for publications
The author approved the manuscript for publication.

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Ethical considerations
Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the author.

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Anatomical Therapeutic Chemical (ATC) Classification. https://www.who.int/tools/atc-ddd-toolkit/atc-classification


hydrochloride (r.c. UA/0907/01/01, UA/10277/01/01, UA/13459/01/01, UA/14033/01/01), since 2015 - Metformin Sandoz (r.c. UA/9477/01/01(02), since 2016 - Metformin Zentiva (r.c. UA/15295/01/01(02)(03), since 2017 - Metformin (r.c. UA/12646/01/01(02)(03), Metformin-Astrapharm (r.c. UA/15739/01/01(02)(03), Metformin Indar (r.c. UA/15947/01/01(02).

- Venlafaxine: This drug is an antidepressant that is actively used to treat obesity in patients with nocturnal incontinence. According to the UGO, its use in complex treatment helps to get rid of an average of 5% of total body weight if used for several weeks. Registered drugs with the active substance venlafaxine in Russia: Alventa, Velaxin, Velafax, Venlaxor, Vensuert, Dapfix, Newvelong, Fevelon and others. In the US, Venlafaxine is sold under Effexor (only available by prescription). Presented in Ukraine: since 2014 - Alventa (r.c. UA/9449/01/01(02)(03), Venlafaxine - 3H (r.c. UA/13809/01/01(02), Venlafaxine hydrochloride (r.c. UA/13446/01/01), Vipax XR (r.c. UA/13444/01/01(02), from 2015 - Venlaksor (r.c. UA/4406/01/01(02), since 2016 - Venlafaxine (r.c. UA/15569/01/01), Venlafaxine hydrochloride (r.c. UA/15123/01/01), Elior (r.c. UA/14972/01/01(02), from 2017 - Velaxin (r.c. UA/3580/02/01(02)(03), from 2018 - Venlafaxine hydrochloride (r.c. UA/16613/01/01).

- Lisdexamphetamine: It is a CNS stimulant that has been widely used in the United States since 2007 to treat attention deficit hyperactivity disorder, especially in children. In studies conducted by the FDA, it was shown that the background of the drug significantly reduces the incidence of psychogenic overeating compared with placebo. In 2015, Lisdexamphetamine in the form of Lisdexamphetamine dimesilate was officially registered with the FDA under the name Vyvanse for the treatment of bulimia (psychogenic overeating).

When analyzing treatment schemes for patients with various manifestations of obesity according to the Pharmacist’s Protocol, it was established that a wide range of over-the-counter drugs, including diuretics, can be dispensed for the treatment of obesity. But the latter should be used with caution and only in case of swelling, because their overdose can provoke kidney failure. There are data on the use of Thyroxine for weight loss in patients with normal thyroid function. However, the use of the latter is potentially dangerous, especially with heart disease. Therefore, it is prescribed only when hypothyroidism and obesity are concomitant pathologies. Dalle Grave et al., 2013, Hruby and Hu 2015, Nuttall 2015, Vasendin 2015, De Lorenzo et al., 2019, Davoudi 2021 and many other authors confirm that there is a wide range of drugs that can be offered to a patient to prevent obesity. However, when using over-the-counter drugs, in order to avoid the consequences of self-medication, you should consult a specialist who will help you understand the advantages and disadvantages of individual drugs, taking into account the individualization of pharmacotherapy. Using the experience of colleagues (Heber, 2003; De Lorenzo et al., 2019; Apovian, 2016; Safaei et al., 2021), we analyzed the herbal medicine market in order to study the existing dosage forms and types of drugs for prevention and treatment of obesity (Shapovalova 2018), but they are the subject of another publication.
ATC-Classification: Copmedium.
http://www.compendium.com.ua/atc/


Davoudi MR. Investigation of the effectiveness of integrated acceptance and commitment therapy (act) and therapeutic regime on food addiction severity index, risky decision making and bmi in adolescent girls with over weight and obesity. Clinical and Experimental Psychology. 2021; 7(11):283.


Obesity. WHO; https://who.int/health-topics/obesity#tab=tab1


