Extemporaneous Preparations in the Pharmacotherapy of Nervous System Disorders: Pharmaceutical Management, Marketing, Analysis, Application

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Abstract. Pharmaceutical management, marketing, pharmaceutical analysis, clinical and pharmacological properties for the use of an extemporaneous drug in the pharmacotherapy of nervous system disorders were studied. The previous experience of the author in the development of new combined drugs of various clinical and pharmacological groups was used. The composition of an extemporaneous drug with sedative pharmacological properties (sodium bromide, novocaine, tincture of valerian) is proposed. The manufacturing technology in pharmacy conditions, qualitative and quantitative indicators of active substances, as well as storage conditions and shelf life of the new extemporaneous drug were developed. The search, development, manufacture in a pharmacy and the use of extemporaneous drugs will contribute to the improvement of planning, organization, and control of the processes of medical and pharmaceutical assistance to patients in conditions of armed conflict. Coordination of medical, pharmaceutical, human, financial, natural, technological, and social resources is necessary to meet the challenges of today.

Keywords: management, marketing, technology, analysis, application, extemporaneous preparation, sedative action.

Introduction. Pharmaceutical development of effective, safe, high-quality, and economically available drugs for diseases of the nervous system is a complex experimental-technological and analytical-pharmacological field. The subsequent introduction of new drugs into industrial production and medical practice requires significant financial costs from the developers. The COVID-19 pandemic revealed the imperfection of the health care sector in the system of pharmaceutical support for patients. Patients of different contingents and age groups were isolated for a long time, stayed at home, less engaged in education, work, social interaction and physical activity. The specified risks negatively affected mental and physical health, caused an increase in mental and neurological health disorders, worsening of accompanying comorbid diseases (depression, addiction, suicides, asthma, tuberculosis, type I and II diabetes, heart attack, stroke, oncology) [1-7].

An analysis of more than 100 applications submitted to the European Medicines Agency shows that various problems can arise in the development of drugs intended for the treatment of disorders of the nervous system. The importance of appropriate early clinical trial design for future development success is emphasized [8].

Pharmaceutical development and research of new drugs for the pharmacotherapy of nervous system disorders is complex. Have a higher failure rate during pharmaceutical development compared to other areas of medicine. The authors carefully examined drug development programs as part of new drug license applications (103 applications, including 57 in neurology and 46 in psychiatry). 74 drugs had a positive conclusion after scientific evaluation; 29 were rejected or withdrawn. Disorders included schizophrenia, depression, Alzheimer's disease, epilepsy, Parkinson's disease, and multiple sclerosis [9].

Previous research has been successful in developing of extemporaneous drugs. Extemporaneous drugs have advantages compared to ready-made drugs: individual dosage, safety, availability [10-22].

In the conditions of armed conflicts, the urgency of finding and manufacturing new formulations of extemporaneous drugs in order to increase the availability and support of combatants, internally displaced persons, and other categories of victims is increasing.

The purpose of the study was to research pharmaceutical management, marketing, analysis, and use of an extemporaneous drug in the pharmacotherapy of nervous system disorders.

Materials and methods. To implement the purpose of the study, a review of the statistical data of the syndicated database of Axioma and the State Service of Ukraine for Medicinal Products and Narcotics regarding the circulation of extemporaneous drugs in the regions of Ukraine was carried out. More than 50 normative and legal documents on the topic of the work (laws, resolutions, orders, orders, instructional and methodical recommendations) were studied and processed. Organizational and legal, regulatory and legal, documentary, technological, chemical, physical and chemical, marketing, comparative, clinical and pharmacological, graphic analysis were used as the research methods.

The research of the article is a fragment of research works of Luhansk State Medical University "Conceptual interdisciplinary approaches to pharmaceutical provision and availability of drugs, taking into account organizational and legal, technological, analytical, pharmacognostic, forensic and pharmaceutical, clinical and pharmacological, pharmacoeconomic, marketing, social and economic competencies" (state registration number 0123U101632, terms 2023-2027); Kharkiv Medical Academy of Postgraduate Education on "Improving the organizational and legal procedure for providing patients with drugs from the standpoint of forensic pharmacy, organization and management of pharmacy" (state registration number 0116U003137, terms 2016-2020) and "Pharmaceutical and medical law: integrated approaches to the system of drug circulation from the standpoint of forensic pharmacy and organization of pharmaceutical business" (state registration number 0121U000031, terms 2021-2026); Petro Mohyla Black Sea National University on the topic "Conceptual interdisciplinary approaches to the drug circulation system, taking into account organizational and legal, technological, biopharmaceutical, analytical, pharmacognostic, forensic and pharmaceutical, clinical and pharmacological, pharmacoeconomic, pharmacotherapeutic aspects" (state registration number 0123U100468, implementation period 2023-2028).

Results and discussion. The failure rate in the development of new drugs targeting important diseases of the central nervous system is high compared to most other areas of drug discovery. At the same time, it should be taken into account [23]:

- low efficiency of penetration through the blood-brain barrier, which is a bottleneck in the development of drugs for the central nervous system;
- drug repositioning factor, which is increasingly popular for finding promising combinations in the development of drugs for the central nervous system.

Pharmaceutical management of new drugs for the nervous system.

The development of new drugs for the treatment of central nervous system (CNS) disorders presents unique challenges compared to other diseases. These include an incomplete understanding of the biology of multifaceted CNS conditions such as Alzheimer's disease, the presence of a blood-brain barrier that limits the flow of molecules to the brain, and the lack of clinically relevant animal models in which to test new drugs [24].

The CNS, which includes the brain and spinal cord, is responsible for coordinating and influencing most functions of the human body. Society has been using drugs that affect the central nervous system for thousands of years. Traditional medicine and rituals have relied on the presence of naturally occurring biologically active compounds in plants and herbs to induce reactions ranging from pain relief to psychedelic hallucinations. CNS drug development programs face a relative lack of fundamental understanding of the underlying disease pathology. Despite this, treatments can be developed that relieve symptoms without stopping or curing the condition, such as antidepressants, including benzodiazepines (e.g., diazepam), selective serotonin.

CNS disorders are severe and complex. Cause high costs for clinical therapy and basic research. Treatment of CNS disorders requires systematic drugs that are able to pass through the brain barrier and affect specific receptors. Until now, such drugs have strong side effects [25, 26].

Addictions to the use of illicit psychoactive substances (cocaine, amphetamines, cannabinoids, opioids) are a serious economic, social, and public health problem in developed countries that can affect many people. Thus, the development of new drugs for the treatment of

cocaine addiction is relevant and necessary. Prospective searches for active substances of plant origin with adaptogenic, anxiolytic, antidepressant, and anti-stress properties (Rhodiola rosea L.). Phytotherapy for users of prohibited psychoactive substances reduces the risk of hip fractures [27].

In emergency situations, in conditions of armed conflict, there are risks that cause the spread of disease. Among the risks: overcrowding, poor hygienic conditions, stress, weakened immune system, lack of, or limited medical and pharmaceutical care. According to social studies, in emergency situations, the use of sedatives can reduce the suffering of victims, relieve stress, and improve the quality of life. The use of extemporaneous hypnotic drugs has medical, pharmaceutical, financial, and social perspectives.

According to the results of studying the composition of extemporaneous preparations, a mixture was proposed [28].

The composition of the mixture has a calming effect on the central nervous system.

Sodium bromide	0.5
Novocaine	0.15
Valerianae tincture	5 drops,
Sugar syrups	20.0
Distilled water ad to	100.0

Technology of preparation in pharmacy.

80 ml of distilled water is measured into the prepared container. Dissolve Sodium bromide in water. Sterilized. Novocaine is then added. After complete dissolution, add 20 ml of Sugar syrupis and 5 drops of Valerianae tincturae. Stir. Strain.

The meaning of the identity of active substances.

Novocaine.

Creation of Schiff bases (Ovchinnikov reaction). A drop of the mixture solution and a drop of diluted hydrochloric acid are placed on a strip of newsprint – an orange color appears.

Sodium ione.

On a graphite rod. Part of the solution is added to a colorless flame. The flame turns yellow.

Bromide ione.

To 5 drops of the solution being analyzed, add 3 drops of diluted sulfuric acid, 0.5 ml of chloroform and drop by shake, 0.1 M solution of potassium permanganate. The chloroform layer turns yellow-brown.

Tinctura Valerianae and Sodium bromide.

2 ml of the solution is evaporated in a water bath. Add 1-2 drops of concentrated sulfuric acid to the dry residue. Brown fumes (sodium bromide) are released. A red-violet color appears (valerian tincture).

Sugar syrupis.

- to 0.5 ml of solution add 2-3 drops of diluted hydrochloric acid, 0.01 g of resorcinol and boil for a minute. A red color appears;
- to 0.5 ml of solution add 3-5 drops of sodium hydroxide solution and 1-2 drops of cobalt nitrate solution. A purple color appears.

Quantitative determination of the active ingredients of the mixture.

Novocaine.

The alkalimetric method is used (hydrochloride): add 10 ml of phenolphthalein-neutralized alcohol to 2 ml of solution and titrate with 0.02 M sodium hydroxide solution until pink color (V1).

1 ml of 0.02 M sodium hydroxide solution corresponds to 0.005456 g of novocaine.

Sodium bromide.

Add 2 drops of diluted nitric acid to the titrated liquid (until the solution becomes discolored) and titrate with a 0.1 M solution of mercuric oxide nitrate (V0). Diphenylcarbazone serves as an indicator. In this case, a total titration of novocaine and sodium bromide is performed. The volume of mercuric oxide nitrate solution used for the titration of sodium bromide is found by the difference in volume: $V_o – V_1/5$.

1 ml of 0.1 M solution of mercuric oxide nitrate corresponds to 0.01029 g of sodium bromide.

Calculate using the following formula (in grams).

$$X\ Novocaine = \frac{V_1 \cdot CF_1 \cdot 0{,}005456 \cdot 120}{2}$$

$$X\ \text{Sodium bromide} = \frac{(V_0 \cdot CF_0 - V_1/5 \cdot CF) \cdot 0{,}01029 \cdot 120}{2}$$

where V_1 – volume of sodium hydroxide titrant;
CF_0 – sodium bromide titrant correction factor;
CF_1 – sodium hydroxide titrant correction factor;
V_0 – volume of titrant of mercury oxide nitrate;
CF – correction factor of mercury nitrate titrant.

Sugar syrupis.

Determine the refractive index of water n0, solution n, and calculate the content of sugar syrup (in milliliters) using the following formula:

$$X = \frac{(n - n_0 - c_1F_1 - c_2F_2) \cdot 100 \cdot 120\ ,}{100 \cdot 0{,}00145 \cdot 64 \cdot 1{,}3}$$

where c_1, c_2 – content of sodium bromide and novocaine, determined by chemical means, %;
F_1, F_2 are the refractive index factors of sodium bromide and novocaine solutions, respectively;
0.00145 – sugar refractive index factor;
64 – sugar concentration in syrup;
1.3 – density of sugar syrup.
Sugar syrupis is prepared by weight, and when preparing dosage forms it is taken by volume.
Storage. In a place protected from direct sunlight, at a temperature not exceeding 15^0C. Shelf life is two days.

Marketing researches.

The market of ready-made preparations was analyzed in order to find analogs of extemporaneous prescription. Established that there are no ready-made preparations of a similar composition in Ukraine (Table 1). Yes, only two preparations (valokormid) are registered with sodium bromide. There were 19 drugs with novocaine (novocaine, menovazin, etc.). With valerian tincture there were 17 drugs (valerian tincture, sedafiton, etc.)

Table 1. Marketing analysis of the drug market with researched active pharmaceutical ingredients.

No.	Active substance	Number of registered medicines
1.	Sodium bromide	2
2.	Novocaine	19
3.	Valerian tincture	17

Application.

At the next stage of the study, the pharmacological properties of active substances for the use of extemporaneous drugs were determined [29].

Noted that sodium bromide strengthens the inhibition processes in the cerebral cortex, restores the balance between the excitation and inhibition processes in case of increased excitability.

Valerian acid has a calming effect on the central nervous system.

Novocaine is a local anesthetic agent with moderate activity and a wide therapeutic range. It reduces or completely suppresses the excitability of nerve fibers, blocks the conduction of impulses

to the central nervous system, which leads to a temporary loss of pain and other types of sensitivity. Reduces spasms of smooth muscles. Reduces the excitability of the heart muscle and motor areas of the cerebral cortex.

The active substances of the extemporaneous drug do not require special conditions for circulation in pharmacies, hospitals, available to consumers [30, 31]. The sedative, anesthetic properties of the extemporaneous drug can be used in the pharmacotherapy of nervous system disorders.

Conclusions. Pharmaceutical management, marketing, pharmaceutical analysis, clinical and pharmacological properties for the use of an extemporaneous drug in the pharmacotherapy of nervous system disorders were studied. The previous experience of the author in the development of new combined drugs of various clinical and pharmacological groups was used. The prospect of manufacturing extemporaneous drugs in pharmacies is substantiated. The pharmaceutical management of new drugs for the nervous system has been developed. The composition of an extemporaneous drug with sedative pharmacological properties (sodium bromide, novocaine, valerian tincture) is proposed. The manufacturing technology in pharmacy conditions, qualitative and quantitative indicators of active substances, as well as storage conditions and shelf life of the new extemporaneous drug were developed. Marketing research has been conducted. Concluded that there are no analogues of the investigated extemporaneous drug on the market. The pharmacological properties of the extemporaneous drug for use in medical practice have been determined. The search, development, manufacture in a pharmacy and the use of extemporaneous drugs will contribute to the improvement of planning, organization, and control of the processes of medical and pharmaceutical assistance to patients in conditions of armed conflict. Coordination of medical, pharmaceutical, human, financial, natural, technological, and social resources is necessary to meet the challenges of today. Further research in the field of work is ongoing.

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