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The treatment of drug-induced rhinitis with an original intranasal combination: Efficacy and safety in experimental animals

E.A. Smolyarchuk[1], Xi Yang[1], V.M. Svistushkin[1], K.V. Eremeeva[1], Zh.M. Kozlova[1], D.A. Kudlay[1, 2, 3], A.S. Machikhin[4], A.V. Guryleva[4], D.A. Derevesnikova[4, 5], A.A. Nedorubov[1]

[1] Sechenov First Moscow State Medical University (Sechenov University), 2, Trubetskaya Str., Bldg 8, Moscow, Russia, 119991
[2] Lomonosov Moscow State University, 1 Leninskie Gory, Moscow, Russia, 119991
[3] State Research Center Institute of Immunology, 24 Kashirskoe Hwy, Moscow, 115522, Russia
[4] Scientific and Technological Centre of Unique Instrumentation of the Russian Academy of Sciences, 15 Butlerova Str., Moscow, Russia, 117342
[5] Bauman Moscow State Technical University, 11 Tverskaya Str., Moscow, Russia, 125009

E-mail: yan9.00@mail.ru

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Rhinitis medicamentosa (RM) is a common complication of prolonged use of nasal decongestants, leading to structural changes in the nasal mucosa. Despite the effectiveness of intranasal glucocorticosteroids, their use may be accompanied by side effects.

Tha aim. To investigate the efficacy and safety of the original combined intranasal therapy consisting of mometasone furoate and dexpanthenol as the main active ingredients in experimental animals.

Materials and methods. An efficacy research was conducted on 18 Chinchilla Soviet rabbits: 3 individuals without RM (control) and 15 individuals with induced RM. The model of induced RM was confirmed by histological examination of the nasal mucosa of 3 randomly selected out of 15 animals after necropsy. The remaining 12 rabbits with RM were divided into 4 groups (n=3): untreated, as well as those with induced RM without treatment, those treated with 5% dexpanthenol, those treated with 0.05% mometasone furoate, and those receiving combination therapy with the two above drugs. RM was induced by administration of 0.1% xylometazoline for 14 days. The safety assessment experiment was conducted on 80 outbred rats (4 groups of 10 females and 10 males each: 3 groups with combined therapy at doses of 50, 200 and 800 µl, respectively, and 4 group (control) with saline) with 28-day intranasal administration. To assess the effectiveness, histological analysis (assessment of structural changes in the nasal mucosa) and photoplethysmography (assessment of the microcirculation of the nasal cavity by cold sampling) were used. To assess the safety of combination therapy, the clinical condition of animals, hematological and biochemical studies, assessment of the hemostasis system, and histological analysis of internal organs were performed.

Results. The histological examination revealed pronounced dystrophic changes in the nasal mucosa in animals with induced MR without treatment, moderate inflammation with dexpanthenol monotherapy and structural restoration in the mometasone furoate monotherapy and combination therapy groups. The best efficacy was observed in the combination therapy group, in which the histological pattern fully corresponded to the structure of the nasal mucosa of healthy animals, in contrast to mometasone furoate monotherapy, where histological signs of incomplete repair were observed. It should be noted that photoplethysmography also confirmed a statistically significant improvement in microcirculation in the combination therapy group compared with the control ($p < 0.05$), approaching the indicators of healthy animals. The results of the study also proved the safety of the original intranasal combination.

Conclusion. The drug combination has demonstrated superiority over monotherapy by the individual components included in its composition, providing hydration and restoration of the nasal mucosa, as well as normalization of microcirculation in it. The photoplethysmography method has shown its effectiveness for noninvasive assessment of blood flow in the nasal

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mucosa. The data obtained substantiate the prospects for further study of the above-mentioned combination therapy with intranasal administration to assess the efficacy and safety of MR treatment in clinical trials.
Keywords: rhinitis medicamentosa; nasal decongestants; mometasone furoate; dexpanthenol; hyaluronic acid; photoplethysmography
Abbreviations: RM — rhinitis medicamentosa; EDTA — ethylenediaminetetraacetic acid; VAS — Visual Analogue Scale; SNOT — Sino-Nasal Outcome Test.

Оригинальная интраназальная комбинация для лечения медикаментозного ринита: оценка эффективности и безопасности на экспериментальных животных

Е.А. Смолярчук[1], Си Янг[1], В.М. Свистушкин[1], К.В. Еремеева[1], Ж.М. Козлова[1], Д.А. Кудлай[1, 2, 3], А.С. Мачихин[4], А.В. Гурылева[4], Д.А. Деревесникова[4, 5], А.А. Недорубов[1]

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет), Россия, 119048, г. Москва, ул. Трубецкая, д. 8, стр. 2
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Московский государственный университет имени М.В. Ломоносова», Россия, 119991, г. Москва, Ленинские горы, д. 1
[3] Федерального государственного бюджетного учреждения «Государственный научный центр “Институт иммунологии”» Федерального медико-биологического агентства, Россия, 115522, г. Москва, Каширское шоссе, д. 24
[4] Федеральное государственное бюджетное учреждение науки «Научно-технологический центр уникального приборостроения» Российской академии наук, Россия, 117342, г. Москва, ул. Бутлерова, д. 15
[5] Федеральное государственное бюджетное образовательное учреждение высшего образования «Московский государственный технический университет имени Н.Э. Баумана (Национальный исследовательский университет)», Россия, 125009, г. Москва, Тверская ул., д. 11 стр. 1

E-mail: yan9.00@mail.ru

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Медикаментозный ринит (МР) — распространённое осложнение длительного применения назальных деконгестантов, приводящее к структурным изменениям слизистой оболочки носа. Несмотря на эффективность интраназальных глюкокортикостероидов, их использование может сопровождаться побочными эффектами.

Цель. Оценить эффективность и безопасность оригинальной комбинированной интраназальной терапии в составе мометазона фуроата и декспантенола в качестве основных действующих веществ на экспериментальных животных.

Материалы и методы. Исследование по изучению эффективности проведено на 18 кроликах породы «шиншилла Советская»: 3 особи без МР (контроль) и 15 особей с индуцированным МР. Модель индуцированного МР была подтверждена гистологическим исследованием слизистой оболочки полости носа у 3 случайно выбранных из 15 животных после некропсии. Оставшиеся 12 кроликов с МР были разделены на 4 группы (n=3): без лечения, а также с индуцированным МР без лечения, с лечением 5% декспантенолом, с лечением 0,05% мометазона фуроатом и получающие комбинированную терапию двумя вышеуказанными препаратами. МР индуцировали введением 0,1% ксилометазолина в течение 14 сут. Эксперимент по оценке безопасности проведён на 80 аутбредных крысах (4 группы по 10 самок и 10 самцов в каждой: 3 группы с введением комбинированной терапии в дозах 50, 200 и 800 мкл соответственно и 4 группа (контроль) с введением физиологического раствора) при 28-дневном интраназальном введении. Для оценки эффективности использовали гистологический анализ (оценка структурных изменений слизистой оболочки полости носа) и фотоплетизмографию (оценка микроциркуляции полости носа холодовой пробой). Для оценки безопасности комбинированной терапии проводили мониторинг клинического состояния животных, гематологические и биохимические исследования, оценку системы гемостаза и гистологический анализ внутренних органов.

Результаты. Проведённое гистологическое исследование выявило выраженные дистрофические изменения слизистой оболочки носа у животных с индуцированным МР без лечения, умеренное воспаление — при монотерапии декспантенолом и восстановление структуры в группах монотерапии мометазона фуроатом и комбинированной терапии. Наилучшая эффективность отмечена в группе комбинированной терапии, у животных которой гистологическая

картина полностью соответствовала структуре слизистой оболочки полости носа здоровых животных, в отличие от монотерапии мометазона фуроатом, где наблюдались гистологические признаки неполной репарации. Следует отметить, что и фотоплетизмография подтвердила статистически достоверное улучшение микроциркуляции в группе комбинированной терапии по сравнению с контролем (p <0,05), приближаясь к показателям здоровых животных. По результатам исследования также была доказана безопасность оригинальной интраназальной комбинации.

Заключение. Лекарственная комбинация продемонстрировала превосходство над монотерапией отдельными компонентами, входящими в ее состав, обеспечивая увлажнение и восстановление слизистой оболочки носа, а также нормализацию микроциркуляции в ней. Метод фотоплетизмографии показал свою эффективность для неинвазивной оценки состояния кровотока в слизистой оболочке полости носа. Полученные данные обосновывают перспективность дальнейшего изучения вышеуказанной комбинированной терапии с интраназальным введением для оценки эффективности и безопасности лечения МР в клинических исследованиях.

Ключевые слова: медикаментозный ринит; назальные деконгестанты; мометазона фуроат; декспантенол; гиалуроновая кислота; фотоплетизмография

Список сокращений: МР — медикаментозный ринит; ЭДТА — этилендиаминтетрауксусная кислота; ВАШ — визуальная аналоговая шкала; SNOT — опросник оценки назальных симптомов.

INTRODUCTION

According to the literature, the problem of nasal obstruction is quite common and occurs in 10–40% of the population [1–3], with more than 200 million people worldwide suffering from non-allergic rhinitis [4].

Regardless of the cause, nasal congestion significantly reduces the quality of life. Topical nasal decongestants (vasoconstrictors, local decongestants, vasoconstrictors, sympathomimetics)[1] are indicated for the treatment of nasal obstruction of any etiology, as indicated in national and international guidelines [5–7]. Over-the-counter availability in pharmacies, rapid achievement of the effect of improving nasal breathing, poor awareness of patients about the possible consequences of unregulated use of nasal decongestants are the reason for their “self-prescription” by patients and uncontrolled use. The state of health that develops against the background of uncontrolled use of nasal decongestants leads to a change in the normal functioning of the nose, which is manifested primarily by difficulty in nasal breathing and is called rhinitis medicamentosa (RM) [8]. This condition is one of the significant causes of nasal obstruction belonging to the group of non-allergic, non-infectious rhinitis [4].

With prolonged exposure of vasoconstrictors to the nasal mucosa, its “remodeling” occurs, which is manifested by tachyphylaxis and “rebound” syndrome [9]. The pathogenesis of this process is contributed by the suppression of the production of endogenous norepinephrine and a decrease in the sensitivity of the smooth muscles of the nasal cavity vessels to it, which is a consequence of a decrease in the number of receptors on the surface of cell membranes of the vascular wall according to the type of negative feedback (down-regulation)[2].

Desensitization of α-adrenergic receptors, which develops against the background of taking the above-mentioned medicine, persists for a long time after the cessation of action. A side effect of uncontrolled use of decongestants is also psychological dependence in patients, which manifests itself in the form of anxiety, headache and anxiety after drug withdrawal (withdrawal syndrome) [10, 11].

Currently, there is no unified strategy for the treatment of RM, despite the good results of using intranasal glucocorticosteroids, which is probably due to the lack of a standardized approach to the design and methods of evaluating the studies. It is also known that intranasal glucocorticosteroids can cause side effects in the form of atrophic changes in the nasal mucosa, dryness, bleeding, crusting and perforation of the nasal septum [12].

THE AIM. Experimental substantiation of the efficacy and safety of the original combined intranasal combination of prolonged action in animals with induced RM.

MATERIALS AND METHODS

The work carried out is a phased experimental study: after substantiation with the help of literature analysis of the combined composition and its further development, the physicochemical properties of the obtained dosage form and preclinical studies to assess the efficacy and safety of the developed combination in animals were studied (Fig. 1 and 2).

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Conditions and duration of the study

The experiment was conducted at Sechenov University from September 2024 to March 2025.

Animals

Experiments to study the specific activity and toxicity of the original drug combination were carried out on rabbits and rats, respectively. The study used 18 sexually mature male rabbits of the "Soviet Chinchilla" breed weighing 3.2–3.5 kg and 80 outbred rats of both sexes (males weighing 200–220 g, females — 180–200 g). The animals were kept in controlled vivarium conditions in accordance with Directive 2010/63/EU, GOST R 1.2.3156-13 and Internal Regulations of the Institution. The sample size of animals was determined in accordance with the "3R" rule, corresponds to the "resource equation" according to Mead, which ensures statistically significant results with the minimum necessary number of individuals in accordance with the principles of bioethics [13]. All manipulations with animals were carried out by trained personnel with necessary qualifications.

Methodology of the experiment

For the experiment, the composition was initially substantiated from the point of view of scientific pharmacological data [14–16], and then an original combined therapy of RM of the following composition was developed for the first time: mometasone furoate — 0.05% and dexpanthenol — 5% as the main substances; hyaluronic acid — 0.5%, hypromellose — 0.5%, EDTA — 0.025%, phosphate buffer to pH=6.8 and purified water to 100% as auxiliary substances.

For experimental work on efficacy assessment (see Fig. 1), a group of 3 animals without RM induction was selected (hereinafter referred to as the "Control" group), 15 rabbits were induced with RM by intranasal administration of 0.1% xylometazoline solution 2 into each nasal passage in a volume of 200 µL/nostril for 2 weeks using a dispenser.

In day 15, 3 rabbits were excluded from the study to confirm the RM model based on the results of histological examination. The nasal cavity with adjacent tissues was isolated and fixed in 10% buffered formalin, decalcified with 10% formic acid, sagittal sections were prepared and stained with hematoxylin-eosin according to the standard method to assess structural changes in the mucous membrane. Attention was paid to structural changes in the nasal mucosa characteristic of RM (dystrophic changes with signs of incipient cell degeneration, focal areas with a reduced number of goblet cells, an increase in the number and size of blood vessels).

After obtaining histological evidence of the development of the RM model, the remaining 12 animals were divided into groups depending on the planned therapy. A group of animals consisting of 3 individuals with an RM model that did not receive therapy (the "No treatment" group) and 9 animals (3 groups of 3 rabbits each) who received intranasally daily for 14 days in a volume of 200 µL/nostril were identified:

- combined therapy with mometasone furoate (0.05%) and dexpanthenol (5%) (main active substances), as well as hyaluronic acid (0.5%) and hypromellose as auxiliary components (the "Combination" group);
- monotherapy with mometasone furoate (0.05%) (the "Mometasone furoate" group);
- monotherapy with dexpanthenol (5%) (the "Dexpanthenol" group).

At the end of the 14-day course of therapy, all animals were removed from the experiment by overdose of anesthesia by intramuscular injection of tiletamine, zolazepam and xylazine. Samples of nasal cavity tissues together with adjacent structures were extracted for histological examination.

A quantitative assessment of the state of microcirculation in the nasal mucosa of rabbits was carried out using the method of photoplethysmography — a non-invasive optical method for studying fluctuations in tissue blood filling by the dynamics of changes in the amount of optical radiation scattered by them [17]. As part of photoplethysmography, using an endoscopic device and a personal computer, images of the area under study were recorded with subsequent digital processing, the result of which was a photoplethysmogram — a periodic signal characterizing fluctuations in the blood volume of the area under study, modulated by cardiac activity [18].

Before the photoplethysmographic study, the animal was anesthetized by intramuscular injection of tiletamine and zolazepam solution at a rate of 15 mg/kg and xylazine solution 1–2 mg/kg. The photoplethysmogram recording began 10 min after anesthesia and was carried out using a probe optical system consisting of a rigid endoscope with a tube diameter of 2 mm and fiber illumination, an eyepiece

lens with a focal length of 50 mm and a high-speed digital color camera (The Imaging Source, Germany). The animal was placed lying on its left side in a stable position. The endoscope was inserted into the right nostril until it touched the mucous membrane with a slight pressure. The optical systems of the endoscope and the eyepiece lens together formed an image of the studied area of the nasal mucosa on the camera's radiation receiver. Images were recorded with a temporal sampling rate of 60 frames/sec. The green channel of the recorded images was further processed in the "MATLAB" environment using an original algorithm, including the steps of averaging the intensity of pixels within the studied area, normalizing the average value and filtering noise components in the frequency range corresponding to the cardiac activity of rabbits (1–10 Hz) [19]. The resulting signal was a photoplethysmogram.

The analysis of changes in tissues on the RM model and subsequent treatment was carried out according to the microcirculation reaction to provocative exposure to cold. Measurements were carried out on the 15th and 29th days from the beginning of the experiment after treatment in accordance with the design. Three series of images for calculating the photoplethysmogram were recorded before and after wetting the studied area with physiological saline at a temperature of 4 ± 1°C. Physiological saline was injected using a syringe with the distal end of the endoscope fixed relative to the area under study, the measurement was carried out 5 minutes after exposure, which is the standard for provocative tests [20].

To study safety, according to GOST 33044-2014 "Principles of Good Laboratory Practice" and Decision of the EEC Council No. 81 dated May 19, 2022, repeated 28-day intranasal administration of the original combination to sexually mature outbred rats of both sexes was carried out. In this case, the studied drug combination was administered in volumes of 50, 200 and 800 µL, and physiological saline (800 µL) was used in the control group. The animals were examined daily with an assessment of their general condition, behavior, autonomic reactions, and appearance. At the end of the course administration of the drug combination, studies of hemostasis parameters, as well as hematological and biochemical analyzes and necropsy with subsequent histological examination of internal organs were carried out.

Ethics approval

For the experimental work, approval was obtained from the Local Ethics Committee of the Sechenov University, Protocol No. 17–24 dated July 04, 2024.

Statistical analysis

For quantitative assessment, the ratio of the amplitude of the photoplethysmogram before and after the provocative test (metric R) was calculated, 3 values for each animal. Statistical processing was carried out using the MATLAB Statistics and Machine Learning Toolbox package, the significance of differences in the R metric between groups of animals was assessed by the threshold $p < 0.05$.

In the experimental part on assessing the safety of the combination, the group arithmetic mean and standard deviation (M ± SD) were calculated for all quantitative parameters. The Kruskal-Wallis test was used as a non-parametric test.

RESULTS

Histological examination

In the control group of animals without any intervention, the nasal mucosa was characterized by the presence of a single-layer multi-row ciliated epithelium, including ciliated and non-ciliated columnar cells, goblet and basal cells, as well as a rich vascularization of the lamina propria with serous glands (Fig. 3).

In RM, pronounced pathological changes in the nasal mucosa are observed, manifested by dystrophic changes in the epithelium with signs of initial degeneration and significant rejection of epithelial cells. In focal areas with a reduced number of goblet cells, a significant increase in neutral mucins is noted with a decrease in acidic mucins, and the vascular component is characterized by a moderate increase in the number and size of blood vessels. Similar reactive changes are observed in the "No treatment" group (Fig. 4).

In all samples of the "Dexpanthenol" group, signs of reactive changes in the nasal mucosa of moderate severity were revealed — minimal dystrophic changes in the epithelium without pronounced rejection and a moderate increase in the number and size of blood vessels (Fig. 5).

The histological picture of the nasal mucosa in the animals of the "Mometasone furoate" (Fig. 6) and "Combination" (Fig. 7) groups corresponded to the histological structure of the microscopic preparations

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of the “Control” group — a variant of the norm for this type, sex and age of animals.

Thus, in a comparative morphological analysis of the nasal mucosa in the “Mometasone furoate” and “Combination” groups, an obvious positive dynamic was revealed in the form of leveling reactive changes after acute damage compared with the “No treatment” group. It should be noted that the results obtained in the “Combination” group differed in significantly less desquamation of the epithelium, better normalization of blood supply and a lower degree of inflammation than in the “Mometasone furoate” group.

The characteristics of the epithelium of the nasal mucosa in the studied groups are presented in Table 1.

To form Table 1, an adapted scale for assessing morphological changes in the nasal mucosa was used, based on a well-known method that includes a scoring assessment of epithelial integrity, vascular reaction and inflammatory infiltrate with translation into an integral damage index [21, 22]. As a result, combined therapy with mometasone furoate and dexpanthenol provided complete restoration of the mucous membrane architecture (integral score 5, which corresponds to the norm), while monotherapy with mometasone furoate showed only partial repair (4 points), monotherapy with dexpanthenol — moderate restoration (2 points). The absence of treatment led to severe dystrophic changes (3 points). These data confirm that combined therapy demonstrates a better reparative effect compared with monotherapy with individual components included in the combination, or the absence of treatment, reflecting the synergism of their anti-inflammatory and regenerative properties.

Photoplethysmography

The results of the analysis and statistical processing of photoplethysmographic data are presented in the boxplot (Fig. 8) and in the summary table 2.

Statistically significant differences in the metric (R) between the “Dexpanthenol” group and the “Control” and “No treatment” groups may be due to moderate restoration of microcirculation in animals receiving dexpanthenol monotherapy. Despite the regenerative properties of dexpanthenol, the absence of an anti-inflammatory component in it probably limited the full restoration of tissues, which was reflected in intermediate values (Me = 1.35), not reaching the level of healthy animals.

In the “Mometasone furoate” group, the absence of significant differences both with the group without treatment (“No treatment”) and with the “Control” group may be due to a significant spread of values (from 0.42 to 2.46), which indicates a heterogeneous reaction of microcirculation in individual individuals. This factor, visualized on the boxplot (see Fig. 8), indicates that mometasone furoate monotherapy, despite the anti-inflammatory effect, does not provide stable restoration of blood flow, which is probably caused by local vasoconstriction or individual variation in sensitivity to glucocorticosteroids.

On the contrary, the “Combination” group demonstrated a significant difference from the “No treatment” group ($p < 0.05$) and no differences with the “Control” group, which confirms the most complete restoration of microcirculation to physiological norm. A decrease in the spread of values (from 0.84 to 1.38) compared with the “Mometasone furoate” group indicates a synergistic effect of the combination: mometasone furoate stops inflammation, and dexpanthenol and hyaluronic acid prevent the development of its side effects, ensuring stable tissue regeneration.

The data obtained during the study demonstrate the possibility of using the photoplethysmography method for an objective assessment of the state of the nasal mucosa when using various methods of RM treatment. However, it should be noted that the establishment of specific quantitative thresholds requires confirmation on a larger sample.

In the safety assessment study, daily 28-day intranasal administration of the combined medicine at doses of 50, 200 and 800 µL did not have any effect on the general condition, behavior, autonomic reactions, condition of the coat, eyes and mucous membranes in rats. Analyzes of body weight (body weight gain with a reliability of p = 0.239), hemostasis system (prothrombin time [PTT] = 22.6 ± 1.1 s in the control group and 22.9 ± 1.4 s in the 800 µl combined solution group, $p = 0.199$), hematological (lymphocyte level from 61.2 to 78.5% with a norm of 57.0–91.0%) and biochemical parameters did not reveal statistically significant changes in all 3 groups compared with the control group, which indicates the absence of an adverse / toxic effect. The histological examination of internal organs (after necropsy) also did not reveal pathological changes, confirming the absence of cytotoxic and local irritant effects of the original medicine combination, which proves its safety with intranasal administration.

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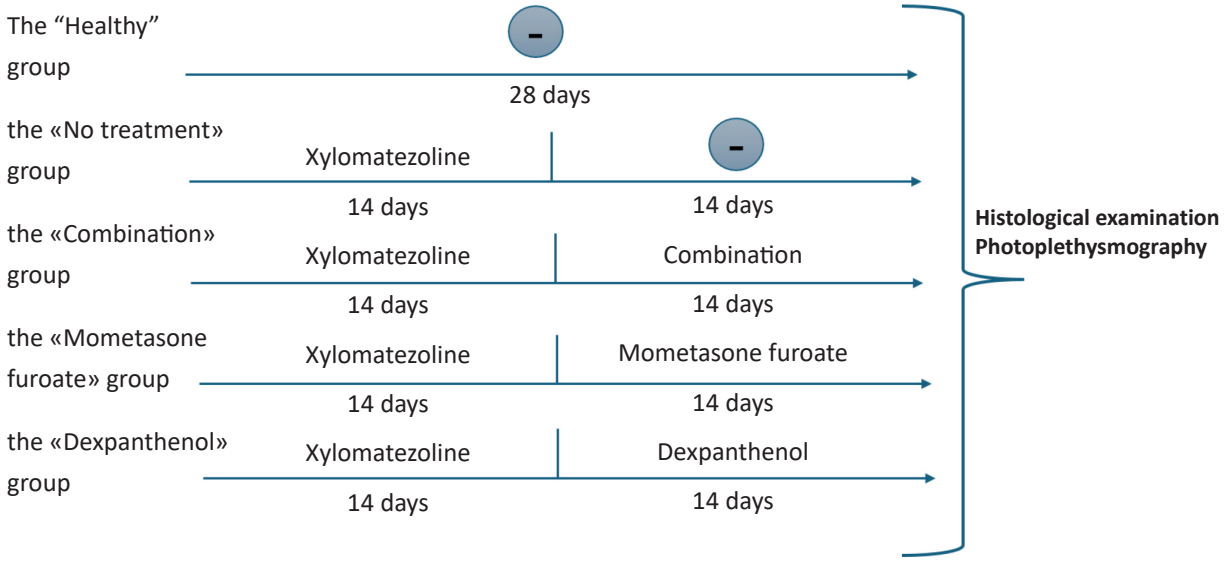

Figure 1 – Design of the experimental part for efficacy assessment.

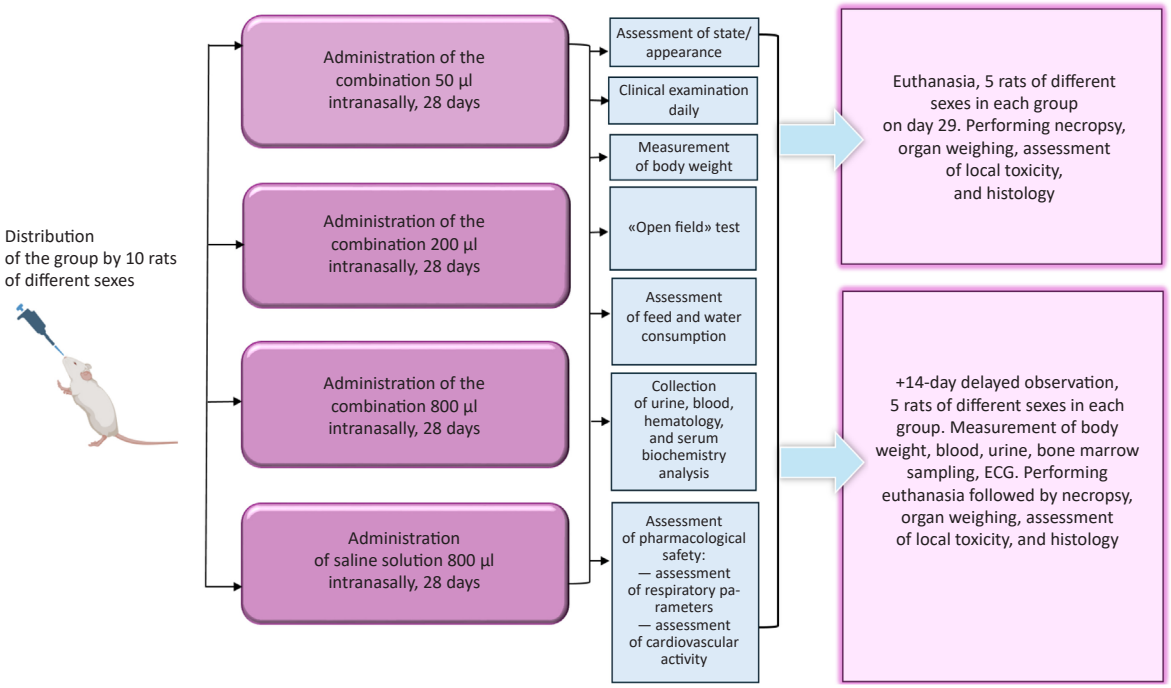

Figure 2 – Design of the experimental part for safety assessment.

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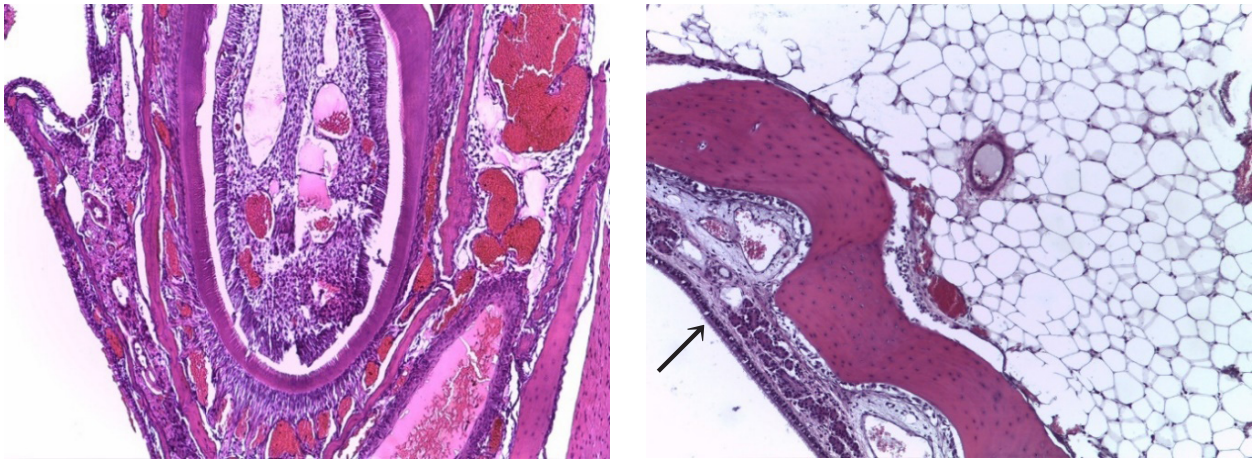
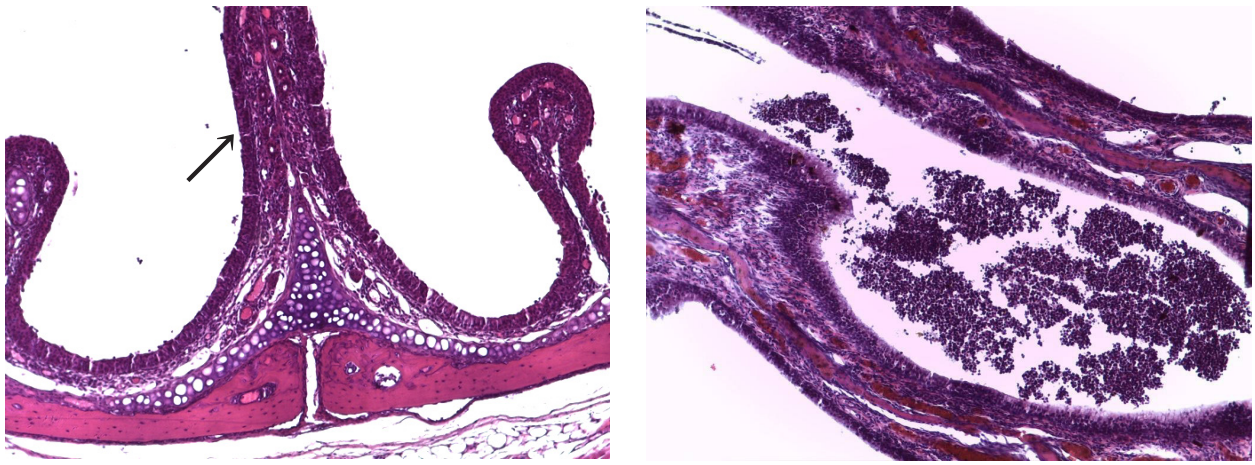


A B

Figure 3 – Microscopic preparation of the nasal cavity. “Control” group.

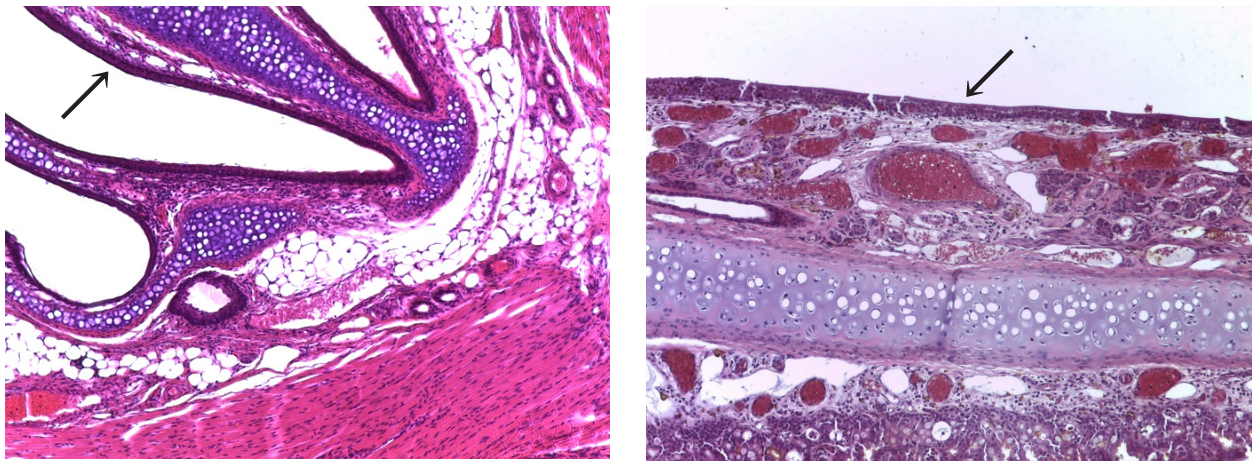
Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.



A B

Figure 4 – Microscopic preparation of the nasal cavity. “No treatment\Control” group.

Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.



A B

Figure 5 – Microscopic preparation of the nasal cavity. “Dexpanthenol” group.

Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.

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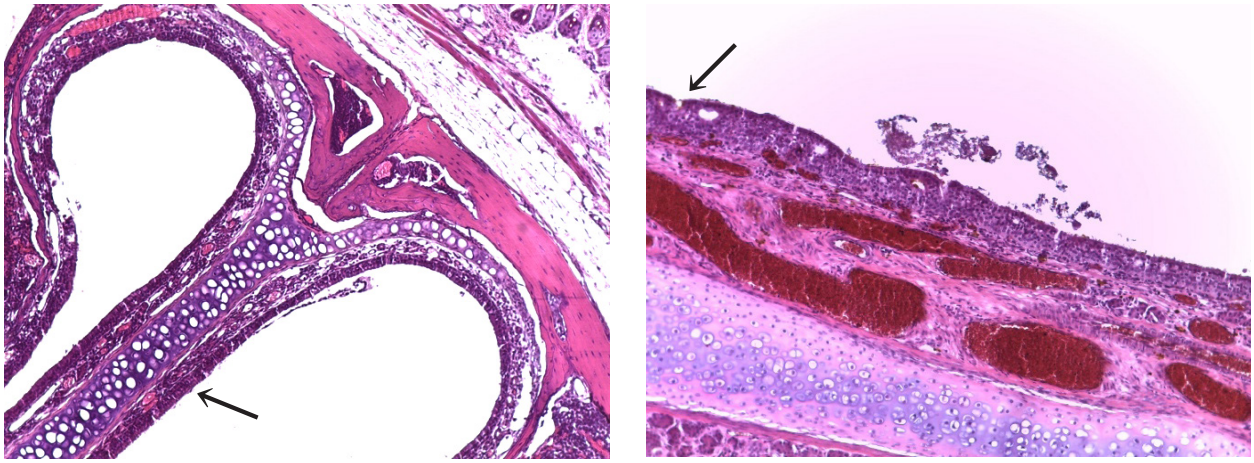
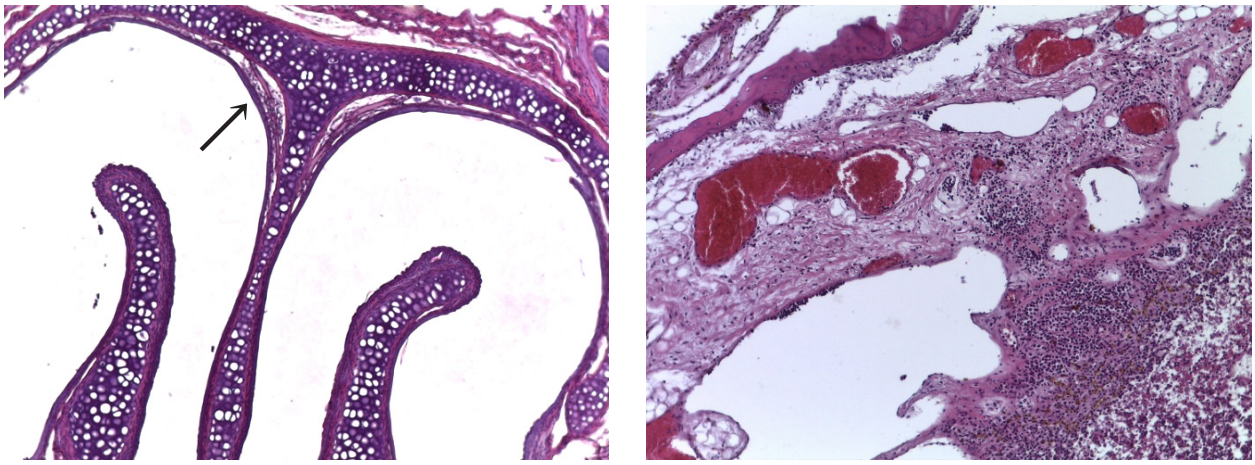


B **B**

Figure 6 – Microscopic preparation of the nasal cavity. “Mometasone furoate” group.

Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.



A **B**

Figure 7 – Microscopic preparation of the nasal cavity. “Combination” group.

Note: A — frontal section, B — sagittal section. Staining: hematoxylin and eosin, magnification ×200; the arrow indicates the epithelium.

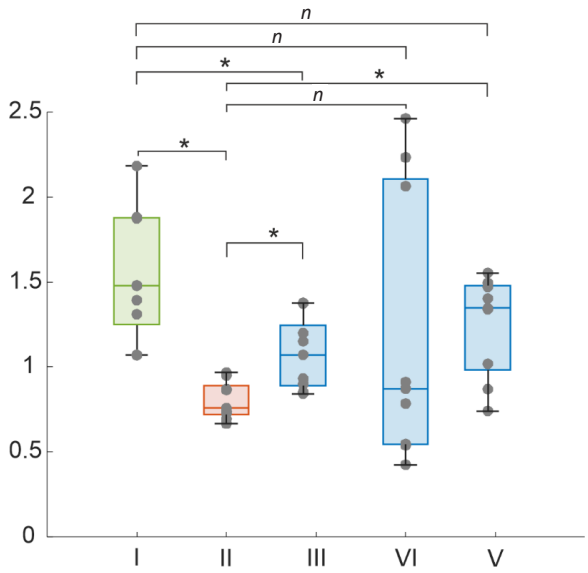


Figure 8 – Boxplot of the ratio of photoplethysmogram amplitudes before and after provocative exposure R.

Note: I — “Control”, II — “No treatment”, III — “Dexpanthenol”, IV — “Mometasone furoate”, V — “Combination”.
* differences are significant at $p < 0.05$. Gray dots indicate the values of the ratio of photoplethysmogram amplitudes before and after provocative exposure for each series.

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Table 1 – Qualitative assessment of the epithelium of the nasal mucosa based on the results of histology

Time frame	Group	Epithelial desquamation	Vascularization	Degree of inflammation	Score
Baseline	Control	Absent	Moderate	Absent	5 (normal)
14 days of RM No treatment	No treatment	Strong	Hyper-expressed	Strong	3 (moderate disorders)
14 days of RM induction + 14 days of treatment	Dexpanthenol	Modearte	Strong	Moderate	2 (severe disorders)
	Mometasone furoate l	Weak	Weak	Minima	4 (minor deviations)
	Combination	Minimal	Weak	Minimal	5 (normal)

Note: RM — rhinitis medicamentosa.

Table 2 – Values of the ratios of photoplethysmogram amplitudes before and after provocative exposure in the studied groups

Group	Ratio of photoplethysmogram amplitudes before and after provocative exposure				
	Me	Min	Max	Confidence interval (95%)	
				Lower	Upper
Control	1.48	1.07	2.18	1.25	1.88
No treatment	0.76	0.67	0.97	0.72	0.89
Dexpanthenol	1.35	0.74	1.55	0.98	1.48
Mometasone furoate	0.87	0.42	2.46	0.55	2.11
Combination	1.07	0.84	1.38	0.89	1.24

DISCUSSION

There is no consensus in the world regarding the treatment tactics of RM. A search of the PubMed (MEDLINE), Cochrane Library, ClinicalTrials.gov databases in the period from 1990 to 2024 revealed only 7 prospective comparative studies on methods of conservative treatment of RM, all of which are devoted to the use of topical intranasal glucocorticosteroids, the action of which is aimed at inhibiting the release of inflammatory mediators. An analysis of the literature showed that fluticasone, budesonide and dexamethasone are used to treat RM [23–25]. According to questionnaires (SNOT, VAS), anterior active rhinomanometry, assessment of mucociliary clearance by saccharin test, these drugs demonstrate high efficacy compared with the control group [26–28]. However, in a study by M. Bende et al. it was noted that already six months after treatment with budesonide — 28% of patients returned to vasoconstrictor intranasal drops [29].

When creating nasal delivery systems, it is necessary to take into account the contact time of the medicine with the mucous membrane (exposure time), which is an important factor affecting the absorption of medicinal substances and prolonging the effect. The vast majority of currently existing medicines are eliminated from the nasal mucosa quite quickly by mucociliary clearance, thereby limiting the adhesion time and the possibility of achieving the maximum therapeutic effect [30–32].

One of the methods to overcome rapid elimination from the nasal mucosa is new technological solutions, namely, drug delivery systems based on mucoadhesive properties, which allow to achieve long-term, controlled retention of the drug at the site of application. Cellulose derivatives are usually used as mucoadhesives [33]. An alternative way to retain at the site of application is to increase viscosity with the help of special excipients, for example, such as hyaluronic acid.

Both of the above-mentioned solutions will allow to achieve a prolonged effect, low toxicity, good mucoadhesive properties, high biocompatibility, indifference, a large range of viscosities, the absence of irritating effect and the ability to biodegrade.

Hypromellose is one of the most commonly used cellulose derivatives in medical practice [33]. When applied to the skin or mucous membranes, hypromellose binds and retains water, forms films and moisturizes the surface at the site of application. Studies have shown that the droplet size of a 0.5% solution in the form of a spray is 20–40 μm, which is acceptable for nasal administration, and a high ability to adhere in principle may indicate good mucoadhesive properties [34]. In addition, hypromellose has demonstrated high efficacy not only as an excipient in the studied combination, but also, probably, as an independent medicinal component (artificial tear), which is used for dry eye syndrome [35].

Hyaluronic acid is a natural polymer and a means of delivering medical substances to the tissues of target cells. Hyaluronic acid has moisturizing properties and the necessary viscosity, which helps to create a protective film in the nasal cavity due to its high ability to retain moisture [36, 37]. Thus, hyaluronic acid provides uniform long-term hydration of the nasal mucosa.

On the problem of pharmacotherapy of RM, only 2 works were found on the effect of mometasone on this pathology in an experiment on animal models. In a study by Tas et al (2005) used mometasone furoate nasal spray for 14 days in guinea pigs. Histological results showed a decrease in edema, an increase in epithelial thickness, the number of goblet cells and the content of glycogen in the stroma, which indicates a decrease in the number of phagocytes [38]. A similar work by Wang et al (2018) on a similar animal model of RM demonstrated restoration of the nasal mucosa after 2 weeks of treatment with mometasone furoate spray [39].

The advantages of taking mometasone furoate in comparison with other intranasal glucosticosteroids are also noted in the treatment of allergic rhinitis. This is explained by its high affinity for glucocorticoid receptors, as well as higher lipophilicity compared with other medicines, which leads to better penetration into the tissues of the nose and paranasal sinuses [40], which, in turn, may be promising for pharmacotherapy of RM.

In the work of Minshall et al it is shown that prolonged use of mometasone furoate does not cause the formation of destructive processes in the mucous membrane, but, on the contrary, contributes to the restoration of the integrity of the epithelial cover of the nasal cavity, as well as the reduction of cellular infiltrates [41].

Despite the above-mentioned advantages of mometasone furoate in comparison with other intranasal glucocorticosteroids, it should be noted the side effects of its topical use, such as: nosebleeds, dryness, atrophic changes in the mucous membrane [42]. However, the frequency of nosebleeds with the use of mometasone furoate (5–8%) is much lower than with the use of other intranasal glucocorticosteroids (up to 15%)[3].

In addition to the effects that have already been described above in relation to the nasal mucosa in the treatment of RM, it is especially important to moisturize it, which can be achieved by using dexpanthenol and auxiliary substances (hyaluronic acid, hypromellose).

[3] Drugs.com. Mometasone Side Effects. Available from: https://www.drugs.com/sfx/mometasone-side-effects.html

Dexpanthenol prevents the negative manifestations of intranasal glucocorticosteroids by stimulating epithelial regeneration and protecting the mucous membrane from the ciliotoxic effect of decongestants [43]. Its ability to restore the barrier function of the nasal mucosa is complemented by the moisturizing properties of hyaluronic acid, which, in turn, not only improves mucociliary clearance, but also participates in reparative processes, which is its positive side compared with synthetic polymers, for example, carbomer [44–46]. Hypromellose, acting as a mucoadhesive agent, prolongs the contact of active components with the mucous membrane, thereby providing a prolonged therapeutic effect. However, it should be noted that careful selection of its concentration is required in order to avoid discomfort during the use [47, 48].

The complementary and mutually reinforcing effects of the components included in the combination allow to achieve more pronounced results compared with monotherapy. Thus, in the “Combination” group, histological analysis revealed the best restoration of the structure of the nasal mucosa, while with isolated use of mometasone furoate, signs of dystrophy, albeit minimal, remained. This once again confirms that dexpanthenol and hyaluronic acid prevent the negative effects of glucocorticosteroids on tissue trophism. However, the combination is not without possible risks: an excess of hyaluronic acid, in turn, can reduce the bioavailability of mometasone furoate, and the lack of data on long-term use requires caution in assessing cumulative effects.

Among the existing analogues, preparations based on hyaluronic acid or dexpanthenol are used mainly for moisturizing, but do not have anti-inflammatory action. Previously studied combinations, including hyaluronic acid with mometasone furoate [49, 50], did not include dexpanthenol, which limited their regenerative potential. Thus, the proposed formula of the intranasal combination is, in fact, not just original, but also unique, combining anti-inflammatory, moisturizing, reparative and mucoadhesive effects.

Despite the relatively small sample, the preclinical study of RM therapy with the original intranasal combination revealed a statistically significant improvement in photoplethysmography indicators, indicating restoration of microcirculation, and also demonstrated normalization of the structure of the nasal mucosa according to histological examination with a high level of safety, which allows recommending it for further study.

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Limitations of the study

Limitations of the study include a relatively small sample of animals. Further studies with an expanded design, increased duration and additional safety assessment methods are recommended for a more complete analysis of the potential effects of the newly developed original medicine combination.

CONCLUSION

The use of the original intranasal combination for the treatment of RM is a new, promising direction in the pharmacotherapy of this disease. The choice of main and auxiliary components is due to their proven anti-inflammatory, regenerative and moisturizing properties. Further study and, possibly, potential implementation in clinical practice will improve control over the course of the disease and minimize the negative impact of nasal decongestants on the condition of not only the nasal mucosa, but also on the quality of life of patients in general. The approbation of a non-invasive quantitative method based on photoplethysmography for analyzing blood flow in the nasal mucosa in modeling RM and its subsequent treatment demonstrated the possibility of using this method in research tasks and in clinical practice.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Elena A. Smolyarchuk — concept, scientific guidance, draft writing—reviewing and editing; Xi Yang — research, methodology development, visualization, writing, draft writing—reviewing and editing; Valery M. Svistushkin — concept, scientific guidance, draft writing—reviewing and editing; Ksenia V. Eremeeva — scientific guidance, methodology development, draft writing—reviewing and editing; Zhanna M. Kozlova — methodology development, manuscript writing (reviewing and editing); Dmitry A. Kudlay — methodology development, draft writing—reviewing and editing; Alexander S. Machikhin — methodology development, draft writing—reviewing and editing; Anastasia V. Guryleva —research conducting, methodology development, graphics visualization, draft writing—reviewing and editing; Darya A. Derevesnikova — research conducting, graphics visualization of , draft writing; Andrey A. Nedorubov — conducting research, developing methodology, draft writing—reviewing and editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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AUTHORS

Elena A. Smolyarchuk — Candidate of Sciences (Medicine), Assistant Professor, Head of the Department of Pharmacology of the A.P. Nelyubin Institute of Pharmacy, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-2615-7167. E-mail: smolyarchuk_e_a@staff.sechenov.ru

Xi Yang — graduate student of the Department of Ear, Throat and Nose Diseases at the Institute of Clinical Medicine of the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0009-0006-2630-7045. E-mail: yan9.00@mail.ru

Valery M. Svistushkin — Doctor of Sciences (Medicine), Professor, Head of the Department of Ear, Throat and Nose Diseases at the Institute of Clinical of

the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0001-7414-1293. E-mail: svvm3@yandex.ru

Ksenia V. Eremeeva — Candidate of Sciences (Medicine), Assistant Professor of the Department of Ear, Throat and Nose Diseases at the Institute of Clinical of the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0001-7071-2415. E-mail: eremeeva_ks@mail.ru

Zhanna M. Kozlova — Candidate of Sciences (Medicine), Assistant Professor of the Department of Pharmaceutical Technology of the A.P. Nelyubin Institute of Pharmacy, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0003-1525-732X. E-mail: kozlova_zh_m@staff.sechenov.ru

Dmitry A. Kudlay — Doctor of Sciences (Medicine), Professor of the Department of Pharmacology at the A.P. Nelyubin Institute of Pharmacy, Sechenov First Moscow State Medical University (Sechenov University); Deputy Dean for Scientific and Technological Development of the Faculty of Bioengineering and Bioinformatics, Senior Researcher at the Faculty of Bioengineering and Bioinformatics, Lomonosov Moscow State University; Leading Researcher of the Laboratory of Personalized Medicine and Molecular Immunology No. 71, State Research Center Institute of Immunology; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0003-1878-4467. E-mail: kudlay_d_a@staff.sechenov.ru

Alexander S. Machikhin — Doctor of Sciences (Technology), Assistant Professor, Leading Researcher, Head of the Laboratory of Acousto-optical Spectroscopy of the Scientific and Technological Centre of Unique Instrumentation of the Russian Academy of Sciences. ORCID ID: 0000-0002-2864-3214. E-mail: machikhin@ntcup.ru

Anastasia V. Guryleva — Candidate of Sciences (Technology), Researcher of the Laboratory of Acousto-optical Spectroscopy of the Scientific and Technological Centre of Unique Instrumentation of the Russian Academy of Sciences. ORCID ID: 0000-0003-2239-3725. E-mail: guryleva.av@ntcup.ru

Darya A. Derevesnikova — student of the Bauman Moscow State Technical University; intern researcher of the Laboratory of Acousto-optical Spectroscopy of the Scientific and Technological Centre of Unique Instrumentation of the Russian Academy of Sciences. ORCID ID: 0009-0001-6452-2620. E-mail: derevesnikova02@bk.ru

Andrey A. Nedorubov — Assistant of the Department of Pharmacology, Head of the Center for Preclinical Research of the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-5915-7999. E-mail: nedorubov.ras@gmail.com

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Screening benzimidazole derivatives for atypical antipsychotic activity

K.Yu. Kalitin[1, 2, 3], O.Yu. Mukha[1, 2], V.B. Voynov[3]

[1] Volgograd State Medical University,
1 Pavshikh Bortsov Sq., Volgograd, Russia, 400066
[2] Scientific Center for Innovative Drugs,
39 Novorossiyskaya Str., Volgograd, Russia, 400087
[3] Southern Federal University,
105/42 Bolshaya Sadovaya Str., Rostov-on-Don, Russia, 344006

E-mail: olay.myha14@gmail.com

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The development of innovative antipsychotic drugs is one of the key tasks of modern pharmacology. Due to their unique chemical properties, benzimidazole derivatives demonstrate diverse neuropsychotropic effects, highlighting their high potential as antipsychotic agents. Bioinformatics methods enable optimization of the process of identifying compounds with high affinity for target receptors.

The aim. To identify and evaluate benzimidazole derivatives with atypical antipsychotic activity using QSAR analysis and pharmacophore modeling, followed by *in vivo* experimental testing in preclinical models of psychotic disorders.

Materials and methods. QSAR models were constructed based on data from 2615 compounds from the ChEMBL database. Pharmacophore modeling was performed based on the structure of the 5-HT2A receptor (PDB ID: 6A94). The antipsychotic activity of the most promising compound was assessed *in vivo* using tests with apomorphine in rats and mice.

Results. Machine learning models were developed and tested to predict the antipsychotic activity of benzimidazole derivatives. The Neural Networks (MAE=0.019) and Random Forest (MAE=0.020) algorithms demonstrated the highest prediction performance. Pharmacophore modeling of interaction with the 5-HT2A receptor identified a promising compound for further testing. Compound RU-31 demonstrated significant reduction (p <0.05) in climbing behavior in mice (ED_{80}=10.16 mg/kg intraperitoneally) and high efficacy when administered with low presynaptic doses of apomorphine (yawning frequency decreased by 49,3% compared to control, p <0.05).

Conclusions. Compound RU-31 showed activity in the climbing test and in the test with low presynaptic doses of apomorphine, suggesting potential atypical antipsychotic effects. Benzimidazole derivative RU-31 is a promising candidate for further investigation in the development of novel atypical antipsychotics.

Keywords: QSAR; pharmacophore modeling; benzimidazole derivatives; antipsychotic activity

Abbreviations: MAE — mean absolute error; MLR — multiple linear regression; NN — neural networks; PLSR — partial least squares regression; QSAR — quantitative structure-activity relationship; SVR — support vector regression; RF — random forest.

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Поиск веществ с атипичной антипсихотической активностью среди производных бензимидазола

К.Ю. Калитин[1, 2, 3], О.Ю. Муха[1, 2], В.Б. Войнов[3]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 400066, г. Волгоград, пл. Павших Борцов, д. 1

[2] Научный центр инновационных лекарственных средств федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 400087, г. Волгоград, ул. Новороссийская, д. 39

[3] Федеральное государственное автономное образовательное учреждение высшего образования «Южный федеральный университет» Россия, 344006, г. Ростов-на-Дону, ул. Большая Садовая, д. 105/42

E-mail: olay.myha14@gmail.com

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Разработка инновационных антипсихотических препаратов является одной из ключевых задач современной фармакологии. Производные бензимидазола, благодаря их уникальным химическим свойствам, демонстрируют широкий спектр нейропсихотропных эффектов и представляют высокий потенциал в качестве антипсихотических агентов. Применение методов биоинформатики позволяет оптимизировать процесс идентификации соединений с высокой аффинностью к целевым рецепторам.

Цель. Провести поиск и оценку производных бензимидазола с атипичной антипсихотической активностью, используя методы QSAR-анализа и фармакофорного моделирования с последующей экспериментальной проверкой *in vivo* на доклинических моделях психотических расстройств.

Материалы и методы. Были построены QSAR-модели на основе данных о 2615 соединениях из базы данных CheMBL. Фармакофорное моделирование проводилось на основе структуры 5-HT2A рецептора (PDB ID: 6A94). Антипсихотическая активность наиболее перспективного соединения была оценена *in vivo* в тестах с апоморфином на крысах и мышах.

Результаты. В ходе исследования были разработаны и протестированы модели машинного обучения для предсказания антипсихотической активности производных бензимидазола. Наилучшие результаты показали нейронные сети (MAE=0,019) и метод случайного леса (MAE=0,020), которые показали высокую точность в прогнозировании активности. Фармакофорное моделирование взаимодействия с 5-HT2A рецептором позволило выделить перспективное соединение для дальнейшего тестирования. Соединение РУ-31 продемонстрировало значительное (p <0,05) снижение вертикализации у мышей ($ЭД^{80}$=10,16 мг/кг внутрибрюшинно), а также высокую эффективность при введении малых пресинаптических доз апоморфина (число зеваний снизилось на 49,3% по сравнению с контролем; p <0,05).

Заключение. Соединение РУ-31 проявило активность в тестах вертикализации и при использовании малых пресинаптических доз апоморфина, что может указывать на его атипичное антипсихотическое действие. Производное бензимидазола РУ-31 является перспективным кандидатом для дальнейшего изучения в рамках разработки новых атипичных антипсихотиков.

Ключевые слова: QSAR; фармакофорное моделирование; производные бензимидазола; антипсихотическая активность

Список сокращений: MAE — средняя абсолютная ошибка; MLR — множественная линейная регрессия; NN — нейронные сети; PLSR — регрессия частичных наименьших квадратов; QSAR — количественное соотношение структура-свойство; SVR — метод опорных векторов; RF — случайный лес.

INTRODUCTION

The search for novel compounds with antipsychotic activity is a key priority in modern pharmacology, particularly in the context of developing drugs for Schizophrenia and other psychotic disorders [1]. Traditional antipsychotic drugs, despite their widespread use, are often associated with serious side effects, including extrapyramidal disorders, metabolic disturbances, and neuroleptic malignant syndrome [1]. These limitations motivate the search for alternative molecules with improved safety and efficacy profiles. Of particular interest is the study of benzimidazole

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derivatives, which, due to their structure, exhibit a broad spectrum of biological activity and may be promising candidates for the creation of new antipsychotics [2].

Benzimidazole derivatives are known for their diverse pharmacological properties, including anticonvulsant [3–5], antidepressant [6], anxiolytic [7], and other neuropsychotropic activity [8, 9]. However, their potential in treating neuropsychiatric diseases, particularly their antipsychotic effects, remains underexplored. Over recent years, study in this area has gained new momentum thanks to the development of molecular modeling and machine learning methods, which can significantly accelerate the process of identifying and evaluating promising compounds. The use of modern tools, such as QSAR analysis and pharmacophore modeling, opens up new possibilities for predicting the activity of substances at the early preclinical stage of development [10]. These methods not only reduce the time required to find new compounds with high affinity for target receptors but also significantly lower the costs associated with expensive biological tests.

The application of machine learning in QSAR analysis allows for the prediction of the biological activity of new chemical compounds based on data from the structure and activity of already known substances. One of the most critical factors for success in this area is the selection of the most appropriate methods capable of identifying the key structural features of compounds responsible for their activity. In this work we use a series of machine learning algorithms, including both linear (multiple linear regression [MLR], partial least squares regression [PLSR]) and non-linear methods (support vector regression [SVR], random forest [RF], neural networks [NN]). This approach will allow for a comparative analysis of the effectiveness of different algorithms and help identify the most suitable ones for this task [11].

The 5-HT_{2A} receptor, whose crystal structure is available in the RCSB PDB database[1], was chosen as a model for pharmacophore analysis. 5-HT_{2A} receptors play a key role in the mechanisms of action of atypical antipsychotics. This makes them a priority target in the development of new drugs for psychotic disorders [12]. These receptors, located predominantly in the cerebral cortex, are involved in regulating dopaminergic and glutamatergic transmission [13], which is directly related to the development of symptoms of Schizophrenia and other psychoses [14, 15]. 5-HT_{2A} receptor antagonists have demonstrated the ability to reduce both positive and negative symptoms of mental disorders while minimizing extrapyramidal side effects, which differentiates them from typical antipsychotics [16].

To assess antipsychotic activity, several apomorphine-based models were used, including hyperactivity, stereotypy, and aggressive behavior in rats, as well as climbing behavior in mice[2]. These models are widely used in pharmacological studies to evaluate both typical and atypical neuroleptics [17]. The use of such models allows not only for the evaluation of the effectiveness of new compounds but also for the identification of their potential side effects, which is an important stage in the development process of new antipsychotics.

THE AIM of this study is to develop and implement a comprehensive approach to the search and evaluation of benzimidazole derivatives with atypical antipsychotic activity, using molecular modeling and machine learning methods. Within this aim, the study involves conducting a QSAR analysis to identify structural features that determine antipsychotic activity, building a pharmacophore model based on interaction with the 5-HT_{2A} receptor, and experimentally evaluating the identified compounds *in vivo* using preclinical models of psychotic disorders.

MATERIALS AND METHODS

Study design

The study design included several sequential stages. In the first stage, QSAR models were built to evaluate a series of benzimidazole derivatives, with the aim of identifying compounds with high affinity for the 5-HT_{2A} receptor, based on data from compounds with established activity. Next, a pharmacophore analysis was conducted based on the 5-HT_{2A} receptor complex with zotepine. This analysis helped identify compounds that best matched the pharmacophore model and select candidates for further testing. In the final stage, the identified lead compound underwent experimental verification of its antipsychotic activity in a series of tests with apomorphine.

QSAR analysis

A dataset was prepared for the study, including 2 615 compounds with known biological activity (IC_{50}), obtained from the ChEMBL database and various literature sources. The validation dataset was formed from compounds obtained from the database

[1] RCSB Protein Data Bank (RCSB PDB). Available from: https://www.rcsb.org/

[2] Ostrovskaya RU, Raevskiy KS, Voronina TA, Garibova TL, Kovalev GI, Kudrin VS, Narkevich VB, Klodt PM. [Methodological recommendations for the study of neuroleptic activity of drugs]. In: [Guidelines for preclinical studies of medicinal products]. Part 1. Moscow: Grif i K; 2012. P. 252–255. Russian

"Benzimidazole derivatives with neurotropic and psychotropic action"[3]. Duplicates were removed, and compounds with missing activity data were filtered out. All biological activity data were converted to micromolar units of IC_{50}.

The chemical structures of the compounds were converted into a machine-readable format (SMILES) using the RDKit package. To calculate molecular descriptors (physicochemical properties, topological indices, geometric properties, electronic characteristics, etc.), the PaDEL-Descriptor Software was used (1875 descriptors for each substance, including 1444 1D, 2D descriptors and 431 3D descriptors). Data processing included removing descriptors with zero variance and high correlation.

The dataset was split into training and test sets in an 80 / 20 ratio. For data, stratified splitting was applied to preserve the activity distribution across the sets. For regression tasks, several machine learning algorithms were selected and tested, including multiple linear regression (MLR), partial least squares regression (PLSR), support vector regression (SVR), random forest (RF), and neural networks (NN). The models were trained on the training dataset. To optimize model parameters and prevent overfitting, 5-fold cross-validation was used.

The performance of the models was evaluated on the validation set by calculating metrics such as the coefficient of determination (R^2) and mean absolute error (MAE) averaged across the 5 folds. Statistical evaluation of performance was carried out by comparing the parameters of the constructed models with those of a baseline regression model. In the final stage, predictive activity estimates (IC_{50}) were obtained for the most promising substances in the test set.

Pharmacophore analysis

Modeling pharmacophores based on the structure of a protein-ligand complex is widely used in the drug development process. The created pharmacophore model helps to understand the critical structural features of the target protein's active site with the ligand, which are necessary for pharmacological activity. In this work, an energy-optimized pharmacophore (e-pharmacophore) was created using the Schrodinger Phase tool, based on a ligand-protein complex. The crystal structure of the $5\text{-}HT_{2A}$ receptor (PDB ID: 6A94) from the Protein Data Bank (RCSB PDB), co-crystallized with zotepine, was chosen to create the pharmacophore model. The Protein Preparation Wizard tool was used for preliminary protein processing, which allows for assigning bond orders, removing water, building missing side chains, and minimizing the protein structure. The pharmacophore hypothesis, obtained using the Phase module, includes features: a hydrogen bond donor (D), an aromatic ring (R), a hydrophobic group (H), and a negative ion (N). Ligands from the database of benzimidazole derivatives with neurotropic activity were tested for compliance with the generated model and evaluated using fitness score, align score, vector score, volume score, and the number of matched features.

In vivo investigation of antipsychotic activity

Test compounds

In animal experiments, the derivative 1-(2-diethylaminoethyl)-2-(4-methoxyphenyl)-imidazo[1,2-a]benzimidazole — compound RU-31 (Research Institute of Physical and Organic Chemistry, Southern Federal University, Russia); clozapine (Organica, Russia); haloperidol (Gedeon Richter, Hungary); and apomorphine (Sigma, USA) were used.

Ethics approval

Animal experiments were conducted in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, the principles of Good Laboratory Practice (GLP) (GOST 33044-2014, 2021), and the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. The study was approved by the Local Ethics Committee of the Volgograd State Medical University (Registration number IRB00005839 IORG0004900, Minutes No. 2024/221 dated April 3, 2024).

Animals

The experiments were performed on male outbred white rats weighing 260–280 g and male outbred white mice weighing 18–25 g. The animals were housed under standard vivarium conditions with a 12-hour light cycle, a temperature range of 22 ± 2 °C, and *ad libitum* access to food and water.

Apomorphine-induced climbing behavior

Mice were divided into four groups of 8 animals each. The experimental groups received intraperitoneal injections of haloperidol, clozapine, compound RU-31 in increasing doses, or saline solution (10 mL/kg, vehicle group). The substances were administered 20 minutes before a subcutaneous injection of apomorphine

[3] Kalitin KY, Mukha OY, Spasov AA, et al. [Benzimidazole derivatives with neurotropic and psychotropic action] [Database]. Certificate of State Registration of a Database No. 2023624590. Russian Federation. Applied Nov 18, 2023; Registered Dec 12, 2023. Copyright holder: Volgograd State Medical University. Russian

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(5 mg/kg). Ten minutes after the apomorphine injection, the animals were placed in cylindrical chambers (height 14 cm, diameter 12 cm, made of 2 mm thick wire rod, with 1 cm spacing between rods) for observation of stereotypical behavior. The intensity of climbing was assessed on a four-point scale: 0 points — no paws on the wire mesh; 1 point — one paw on the mesh; 2 points — two paws on the mesh; 3 points — three paws on the mesh; 4 points — four paws on the mesh. The assessment was performed every 2 min for 10 s over a one-hour period. At the end of the experiment, the total score for each animal was calculated.

Dose-response curves were constructed, from which the ED_{80} values for each compound were interpolated. The analysis was performed using non-linear regression with a variable slope model and calculation of the coefficients of determination (R^2). The obtained ED_{80} values were used in further experiments.

Apomorphine-induced hyperactivity in the Open field test

Rats were divided into four groups of 8 animals each. Thirty minutes before the apomorphine injection, the following were administered intraperitoneally: saline (10 mL/kg, vehicle), haloperidol (1 mg/kg), clozapine (7.5 mg/kg), or compound RU-31 (10 mg/kg). Apomorphine was administered subcutaneously (5 mg/kg) 3 minbefore testing. Horizontal motor activity was recorded in the Open field apparatus for 5 min after the apomorphine injection.

Effect on stereotyped behavior induced by apomorphine

Rats were divided into four groups of 8 animals each. Thirty minutes before the apomorphine injection, the following were administered intraperitoneally: saline (10 mL/kg, vehicle group), haloperidol (1 mg/kg), clozapine (7.5 mg/kg), or compound RU-31 (10 mg/kg). Apomorphine was administered subcutaneously (1 mg/kg). Stereotyped behavior was assessed every 15 min for 2 ho on a three-point scale (1 — weak, 2 — moderate, 3 — intense stereotypy).

Effect on the effects of low (presynaptic) doses of apomorphine

Animals were divided into four groups of 10 individuals each. Thirty minutes before the apomorphine injection, rats received intraperitoneal injections of: saline (10 mL/kg), haloperidol (1 mg/kg), clozapine (7.5 mg/kg), or compound RU-31 (10 mg/kg). Apomorphine was administered subcutaneously (0.1 mg/kg). The number of yawning movements for each animal was recorded over 60 min.

Effect of substances on aggressive behavior

The same pairs of animals were used throughout the study, with pairs always selected from adjacent cages and receiving the same therapy. To induce aggressive behavior, rats were administered apomorphine (1 mg/kg, s.c.) daily for 15 days. Aggressive behavior was assessed on days 1, 3, 6, 9 and 12 of the experiment. The following were observed: (1) latency period (time to the first attack or first aggressive posture) and (2) intensity of aggressive behavior using a four-point scale: 0 — no aggression; 1 — weak aggression without vocalization; 2 — intense aggression with vocalization but without biting; 3 — continuous attacks or attempts to bite. The test was stopped upon reaching the maximum level of aggression to avoid injury. Animals not showing aggressive behavior by day 15 were excluded from further study. On day 15, the study of the effect of the test compounds on apomorphine-induced aggression began. Haloperidol (1 mg/kg, n = 8), clozapine (7.5 mg/kg, n = 8), compound RU-31 (10 mg/kg, n = 8), or saline solution (10 mL/kg, n = 8) were administered intraperitoneally 30 min before the apomorphine injection (1 mg/kg, s.c.). Immediately after the apomorphine injection, pairs of rats were placed in a testing cage, and aggressive behavior was recorded for 15 min.

Statistical analysis

GraphPad Prism 10.1 with an academic license (Dotmatics, USA) was used for data processing. After checking for normality of distribution using the Shapiro–Wilk test, group comparisons were performed using one-way ANOVA with Dunnett's *post hoc* test for normally distributed data, and the Kruskal–Wallis test with Dunn's post hoc test for non-normally distributed data. Differences between groups were considered statistically significant at $p < 0.05$.

RESULTS

QSAR analysis

Table 1 presents the performance evaluation results of various machine learning models on the test and validation datasets. For each model, the mean absolute error (MAE), coefficient of determination (R^2), and *p-value*, reflecting the statistical significance of the metrics compared to a baseline regression model, were calculated. All considered models showed statistically significant results ($p < 0.05$), confirming their applicability to this task.

Table 1 – Performance evaluation of models on the test and validation datasets

Model		MAE	R^2	*p*-value
MLR	Test	0.01645	0.87	< 0.05
	Validation	0.02323	0.76	< 0.05
PLSR	Test	0.01593	0.89	< 0.05
	Validation	0.02188	0.80	< 0.05
SVR	Test	0.01471	0.91	< 0.05
	Validation	0.01974	0.83	< 0.05
RF	Test	0.01453	0.91	< 0.05
	Validation	0.01961	0.84	< 0.05
NN	Test	0.01405	0.92	< 0.05
	Validation	0.01920	0.85	< 0.05

Note: the *p*-value reflects the statistical significance of the model's metrics compared to a baseline regression model.

Table 2 – Activity prediction for compounds

Model	IC_{50} RU-31 (μM)	IC_{50} RU-30 (μM)	IC_{50} RU-204 (μM)
MLR	0.066	0.074	0.167
PLSR	0.067	0.081	0.165
SVR	0.064	0.079	0.164
RF	0.062	0.076	0.167
NN	0.063	0.074	0.164
Experiment[4]	0.044	0.069	0.15

Table 3 – Codes of the most promising substances and their chemical structures

Compound	IUPAC	SMILES
RU-30	2-(2-(4-ethoxyphenyl)-9*H*-benzo[d]imidazo[1,2-a] imidazol-9-yl)-*N*,*N*-diethylethan-1-amine	CCOC1=CC=C(C=C1)C4=C[N]3C2=C(C=CC=C2)[N] (CCN(CC)CC)C3=N4
RU-31	*N*,*N*-diethyl-2-(2-(4-methoxyphenyl)-9*H*-benzo[d] imidazo[1,2-a]imidazol-9-yl)ethan-1-amine	CCN(CC)CC[N]3C1=C(C=CC=C1)[N]4C=C(C2=CC=C(C=C2) OC)N=C34
RU-204	*N*,*N*-diethyl-2-(2-(thiophen-2-yl)-9*H*-benzo[d] imidazo[1,2-a]imidazol-9-yl)ethan-1-amine	CCN(CC)CC[N]3C1=CC=CC=C1[N]4C=C(C2=CC=CS2) N=C34

Table 4 – Screening results of benzimidazole derivatives for compliance with the pharmacophore hypothesis

Compound	Matched ligand sites	Align Score	Vector Score	Volume Score	Fitness Score
RU-31	3	0.795	0.828	0.231	1.013
RU-30	3	0.879	0.838	0.225	0.989
RU-204	2	0.313	0	0	0.208

Table 5 – Effect of haloperidol (1 mg/kg), clozapine (7.5 mg/kg), and compound RU-31 (10 mg/kg) on yawning behavior in rats induced by low doses of apomorphine (0.1 mg/kg)

Group	Number of yawns	*p*-value
Vehicle	24.3 ± 3.4	–
Haloperidol	4.5 ± 1.3	< 0.05
Clozapine	8.324 ± 2.2	< 0.05
Compound RU-31	12.324 ± 6.8	< 0.05

Note: data are presented as mean ± SEM.

[4] Yakovlev DS. [Condensed azoles as a new class of serotonin receptor ligands] [dissertation for the degree of Doctor of Medical Sciences]. Volgograd; 2016. 98 p. Russian

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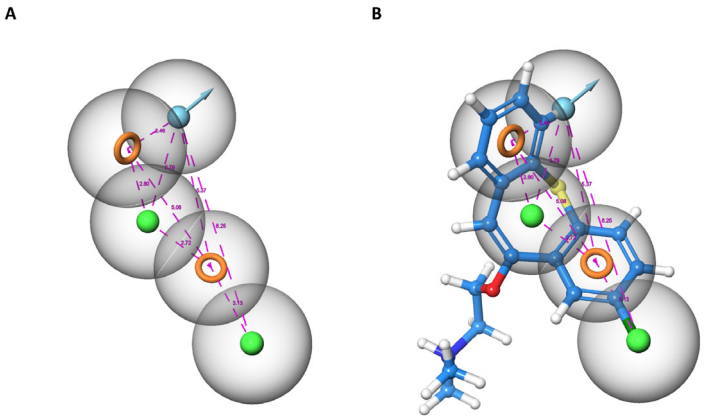

Figure 1 – Pharmacophore model for 5-HT2A receptor antagonism, based on the receptor-ligand complex structure, with five features: one hydrogen bond donor (blue sphere), two hydrophobic sites (green spheres), and two aromatic rings (orange rings) [A] and the distance between zotepine's pharmacophore features in angstroms [B]

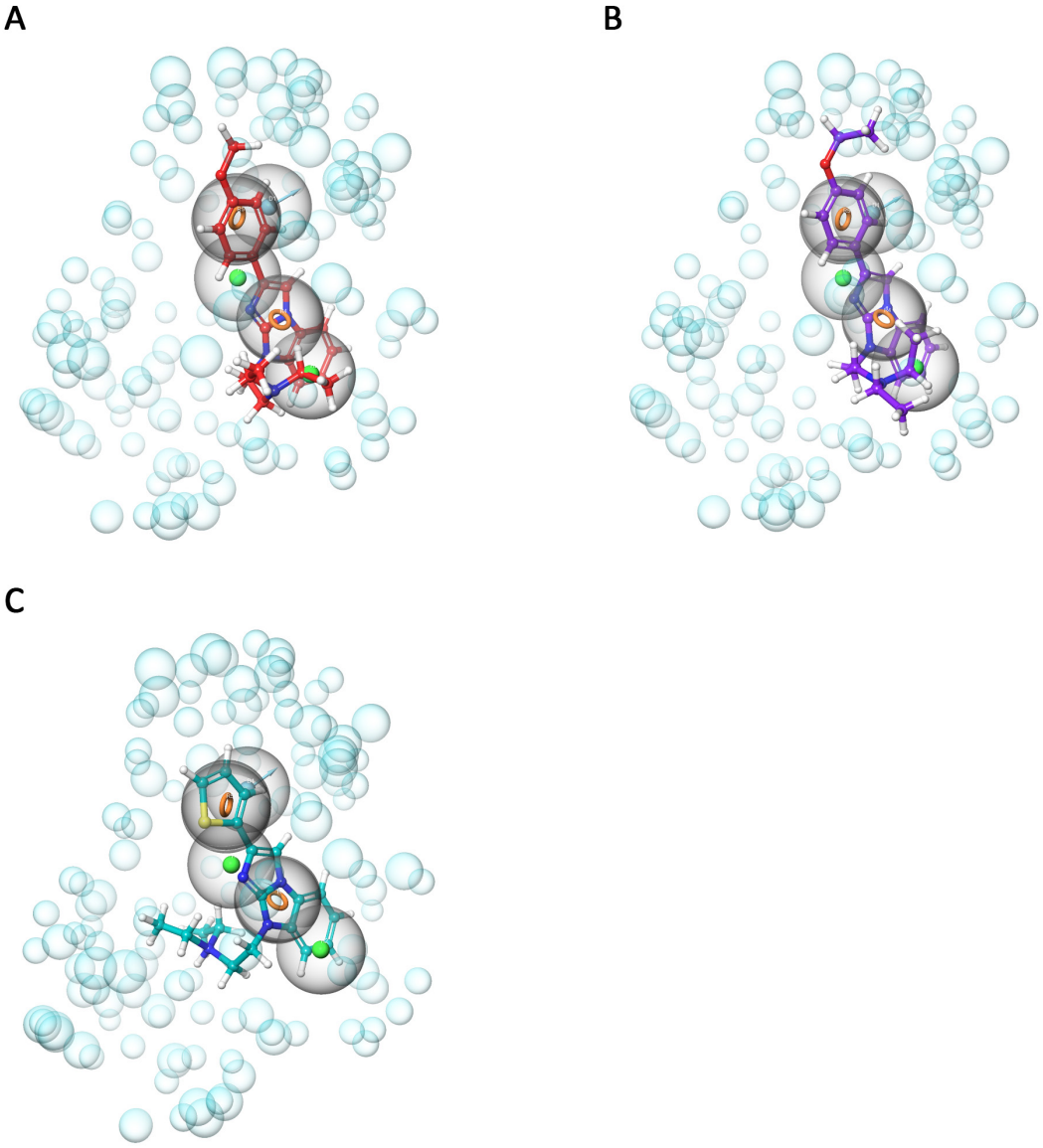

Figure 2 – Alignment of the DHHRR pharmacophore hypothesis with benzimidazole derivatives RU-31 [A], RU-30 [B], and RU-204 [C].

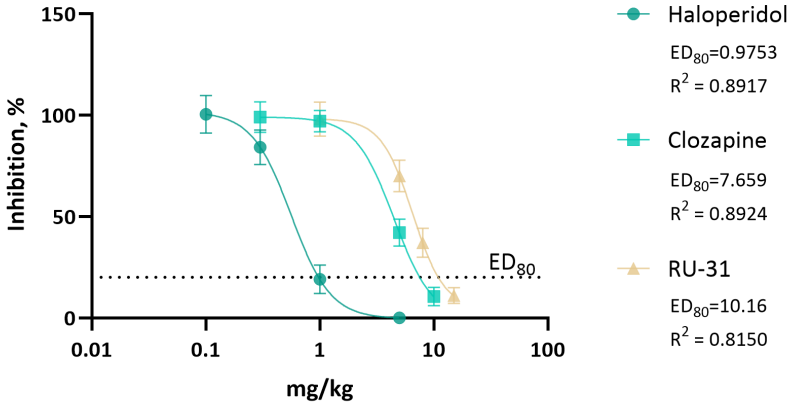

Figure 3 – Dose-response curves for increasing doses (i.p.) of haloperidol, clozapine, and compound RU-31 in the climbing test in mice with stereotypic disorder induced by a single injection of apomorphine (5 mg/kg).

Note: data are presented as mean ± SEM.

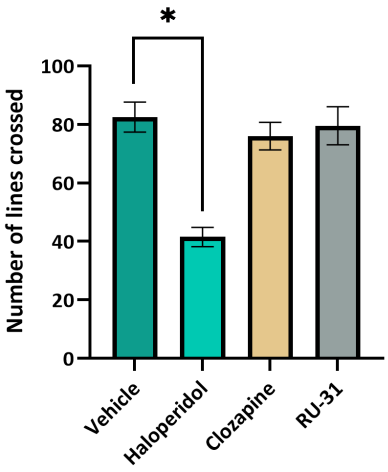

Figure 4 – Effect of haloperidol (1 mg/kg), clozapine (7.5 mg/kg), and compound RU-31 (10 mg/kg) on hyperactivity in rats induced by apomorphine (5 mg/kg).

Note: data are presented as mean ± SEM. Differences are statistically significant relative to the vehicle group: * — $p < 0.05$.

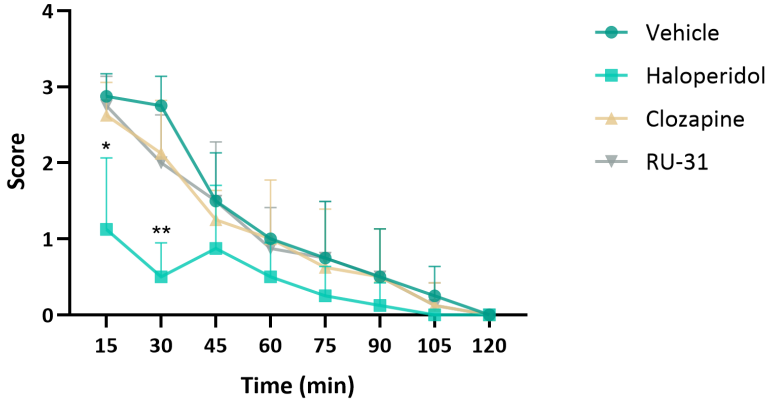

Figure 5 – Effect of haloperidol (1 mg/kg), clozapine (7.5 mg/kg), and compound RU-31 (10 mg/kg) on stereotyped behavior in rats induced by apomorphine (1 mg/kg).

Note: data are presented as mean ± 95% CI. Differences are statistically significant relative to the vehicle group: * — $p < 0.05$; ** — $p < 0.01$.

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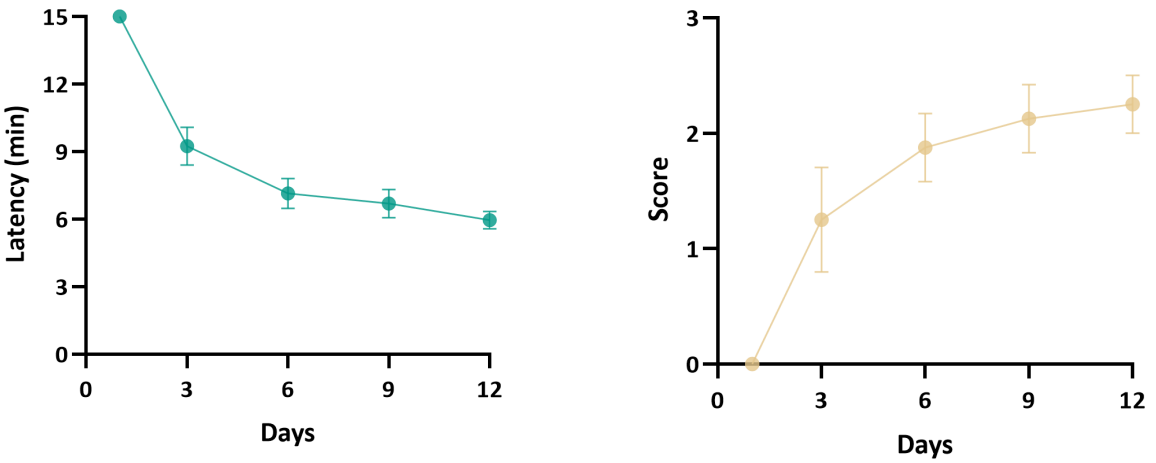

Figure 6 – Dynamics of aggressive behavior indicators in rats induced by apomorphine (1 mg/kg) before the administration of substances with antipsychotic activity.
Note: Data are presented as mean ± SEM.

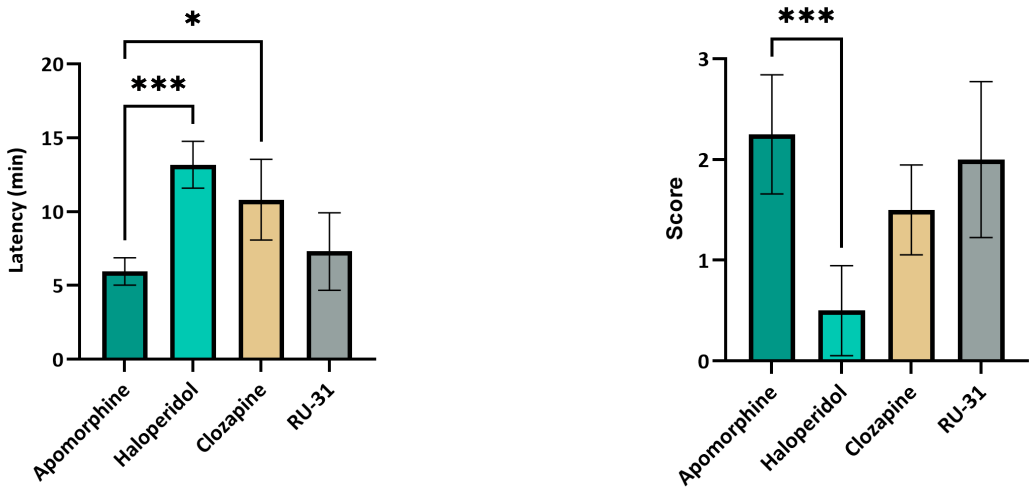

Figure 7 – Effect of haloperidol (1 mg/kg), clozapine (7.5 mg/kg), and compound RU-31 (10 mg/kg) on aggressive behavior in rats induced by apomorphine (1 mg/kg).
Note: Data are presented as mean ± 95% CI. Differences are statistically significant relative to the vehicle group: * — p <0.05; *** — p <0.001.

Among all models, the NN demonstrated the best performance on both the test and validation datasets. It provided the lowest MAE of 0.01405 and 0.01920, respectively, and the highest R^2 — 0.92 and 0.85. This indicates the NNs ability to most accurately capture complex non-linear dependencies in the data.

The RF and SVR models showed comparable results, slightly inferior to the NN. The PLSR and MLR methods demonstrated the least accurate results among the models considered.

It is worth noting that all models showed some performance degradation on the validation set compared to the test set, which is expected and indicates the absence of significant overfitting. Overall, the results suggest the superiority of more complex non-linear models, such as NNs and ensemble methods, for solving this prediction task.

The results in Table 2 reflect the predicted activity values (IC_{50}) for three compounds (RU-31, RU-30, and RU-204; Table 3), obtained using five different machine learning models (MLR, PLSR, SVR, RF, and NN). The table also includes experimental IC_{50} values for comparison.

Analyzing the predicted IC_{50} values, it can be noted that all models provide quite similar results for each compound. For compound RU-31, the predicted values range from 0.062 to 0.067 μM, for RU-30 — from 0.074 to 0.081 μM, and for RU-204 — from 0.164 to

0.167 μM. For compounds RU-31, RU-30, and RU-204, the difference between predicted and experimental values is 0.018–0.023, 0.005–0.012 and 0.014–0.017 μM, respectively.

Among the models considered, the RF and NN models provide the most accurate predictions. Their predicted values are closest to the experimental data for all three compounds. This is consistent with the results obtained on the test and validation sets, where these models also showed the best performance.

Pharmacophore modeling

The five-feature (DHHRR) pharmacophore model, derived using the protein-ligand complex of the serotonin 2A receptor and zotepine (PDB ID: 6A94), is presented in Figure 1.

Table 4 presents the screening results of benzimidazole derivatives for compliance with the pharmacophore hypothesis. Ligands were selected based on matching sites and fitness scores. Compound RU-31 demonstrated the best fitness score of 1.013 with three matching ligand sites. Compound RU-30 also had three matching ligand sites and showed a fitness score of 0.989. Compound RU-204 had two matching ligand sites and a fitness score of 0.208. These data show that benzimidazole derivatives such as RU-31 and RU-30 have a high degree of compliance with the pharmacophore hypothesis compared to RU-204. Figure 2 also shows the alignment of the pharmacophore hypothesis with the studied ligands.

Effect on apomorphine-induced climbing

In the experiment, dose-response curves were obtained for haloperidol, clozapine, and compound RU-31 in the apomorphine-induced climbing model in mice (Fig. 3). The potential antipsychotic activity of the compounds was assessed based on the suppression of stereotypical behavior induced by apomorphine.

Haloperidol showed the highest efficacy among the tested compounds, with an ED_{80} of 0.9753 mg/kg and a R^2 of 0.8917, indicating a high correlation between dose and effect. Clozapine demonstrated intermediate efficacy with an ED_{80} of 7,659 mg/kg and R^2 = 0.8924. Compound RU-31 showed activity close to that of clozapine, with an ED_{80} = 10,16 mg/kg and a coefficient of determination of 0.8150.

These results demonstrate that haloperidol, as a typical antipsychotic, most effectively suppressed dopamine-mediated stereotyped behavior, while clozapine and compound RU-31 showed a less pronounced effect. The obtained ED_{80} values for all compounds were used for further pharmacological studies.

Apomorphine-induced hyperactivity in rats in the Open field test

Figure 4 presents the results of the study on apomorphine-induced hyperactivity in rats in the Open field test after compound administration. The graph shows the level of motor activity in rats, expressed as the number of lines crossed on the field's arena. In the vehicle-treated group, high motor activity was observed. The administration of haloperidol (1 mg/kg) significantly reduced the number of lines crossed, indicating its pronounced inhibitory effect on motor activity, likely due to the blockade of dopamine receptors. In the group receiving clozapine (7.5 mg/kg), motor activity was not reduced compared to the vehicle group. The administration of compound RU-31 (10 mg/kg) also did not lead to a significant change in the number of lines crossed compared to the vehicle group. This may suggest its neutral effect on the motor activity of rats in this experiment, a characteristic of substances with atypical antipsychotic activity similar to clozapine.

Effect on stereotyped behavior induced by apomorphine

Figure 5 shows the effects of haloperidol (1 mg/kg), clozapine (7.5 mg/kg), and compound RU-31 (10 mg/kg) on apomorphine-induced stereotypy in animals over 120 min. In the vehicle group, a gradual decrease in the level of stereotypy is observed, with maximum values in the first 15 min and a gradual reduction to minimum values by the 120 min.

At 15 min after haloperidol administration, the level of stereotypy is significantly reduced ($p < 0.05$ compared to vehicle). At 30 min, this reduction becomes even more pronounced ($p < 0.01$ compared to vehicle). Throughout the observation period, haloperidol maintains a reduced level of stereotypy, most pronounced in the first 30 min. During the first 45 min of observation, clozapine shows a slight tendency to reduce the level of stereotypy compared to the vehicle. After 45 min, the levels of stereotypy under the influence of clozapine approach the vehicle values.

Compound RU-31 has no statistically significant

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effect on the level of stereotypy. Throughout the observation period, the levels of stereotypy under the influence of RU-31 remain close to the vehicle values, with minor deviations at 30 min.

Effect on the effects of low (presynaptic) doses of apomorphine

According to the obtained data (Table 5), in the group receiving haloperidol (1 mg/kg), the number of yawns decreased by 81.5%, which is significantly less than the vehicle level ($p < 0.05$). In the group receiving clozapine (7.5 mg/kg), the number of yawns decreased by 65.7%, which is also significantly lower compared to the vehicle group ($p < 0.05$). In the group receiving compound RU-31 (10 mg/kg), the average number of yawns was 49.3% less than in the vehicle group ($p < 0.05$). Thus, all studied compounds statistically significantly reduced the number of yawns compared to the vehicle group, indicating the presence of antipsychotic activity. The high specificity of the test is explained by the fact that serotonin receptor antagonists do not have a direct effect on dopamine receptors but can influence the level of dopamine in synapses by reducing its secretion. This effect is not apparent in tests with high doses of apomorphine, as in that case, the effect on mediator release is not significant.

Effect of substances on aggressive behavior

Figure 6 shows the dynamics of changes in the aggressive behavior of rats under the influence of apomorphine over 12 days. The left graph shows the latency period (time to the first aggressive reaction), which gradually decreases from 15 to 6 min. The right graph illustrates the severity of aggression in scores, which increases from 0 to 2 or more points by day 12, also indicating an intensification of aggressive reactions.

Figure 7 shows the effect of the test compounds on aggressive behavior on day 15 of the experiment. On the left diagram, it can be noted that haloperidol (1 mg/kg) significantly increases the latency period compared to the vehicle ($p < 0,001$). Clozapine (7.5 mg/kg) also significantly increases the latency period ($p < 0,05$), but this increase is less pronounced compared to haloperidol. The latency period in the group receiving compound RU-31 (10 mg/kg) does not differ significantly from the vehicle.

The right diagram shows the effect of the substances on the intensity of aggression. Haloperidol significantly reduces aggression scores compared to the vehicle ($p < 0.001$), while clozapine and compound RU-31 do not have a significant effect on this indicator.

DISCUSSION

The obtained results demonstrate high predictive efficacy of machine learning models in assessing the 5-HT_{2A}-antagonistic activity of benzimidazole derivatives. In particular, the NN and RF methods showed the best performance in terms of accuracy and predictive significance among all tested models. This suggests the utility of employing more complex algorithms for analyzing data on the biological activity of substances, as they are capable of accounting for complex non-linear dependencies in molecular descriptors, which significantly enhances the quality of prediction [18, 19].

The significant correlation between the predicted and experimental IC_{50} values for compounds RU-31, RU-30, and RU-204 confirms the validity of the developed models. However, some deviations from the experimental data indicate the potential for further optimization of the models and the inclusion of additional factors that influence the activity of the substances.

Pharmacophore analysis revealed important structural features of benzimidazole derivatives that mediate interaction with 5-HT2A receptors [20]. Compounds RU-31 and RU-30 showed the highest degree of compliance with the pharmacophore model, which corroborates their high affinity for this receptor. These results are consistent with the *in vivo* experimental data, where compound RU-31 demonstrated significant antipsychotic activity.

The obtained QSAR and pharmacophore models have high potential for future use in the search for new active ligands with antagonistic activity towards 5-HT_{2A} receptors. In particular, these models can be successfully applied for the rational design and optimization of new benzimidazole derivatives capable of interacting with 5-HT_{2A} receptors.

Experiments with apomorphine, aimed at assessing the antipsychotic activity of the tested compounds, confirmed the efficacy of RU-31 in several behavioral tests in animals. Compound RU-31 significantly reduced apomorphine-induced climbing in mice, indicating its ability to block the dopaminergic influence. However, in the apomorphine-induced stereotypy experiment,

the effect of compound RU-31 and clozapine did not differ from the vehicle, which corresponds to previously obtained data for the compound MDL 100 907 [21, 22] and trazodone [23]. In the Open field test, compound RU-31 did not exert a significant effect on the motor activity of rats. Similar results were obtained for ketanserin [24]. This suggests that RU-31 may have a more favorable side-effect profile compared to typical antipsychotics like haloperidol, which often cause pronounced motor depression [25].

In contrast to haloperidol, which significantly suppressed aggressive reactions, RU-31 did not have a significant impact on this indicator. This result may be explained by the fact that compound RU-31 affects the dopaminergic system through pathways different from those of typical antipsychotics, which is characteristic of atypical antipsychotic agents. However, the lack of effect on aggression may indicate a limitation of its action regarding certain behavioral aspects associated with psychoses and requires further investigation.

The obtained results also demonstrate the potential of RU-31 as an antipsychotic with a low risk of extrapyramidal side effects [26]. In tests with low doses of apomorphine, aimed at assessing presynaptic effects, compound RU-31 statistically significantly reduced the number of yawning movements. However, this effect was less pronounced compared to haloperidol and clozapine, which is likely due to the lack of direct action on dopamine receptors and, consequently, a lower risk of developing extrapyramidal disorders. The obtained results are consistent with a previous study where it was shown that the serotonin receptor antagonists ritanserin and ketanserin do not affect aggressive behavior [27, 28].

Comparing the results obtained for RU-31 with those for haloperidol and clozapine allows us to conclude that compound RU-31 has characteristics similar to atypical antipsychotics. The studied substance reduces the severity of climbing and yawning behavior, while not significantly affecting motor activity and aggression. In aggregate, these properties make compound RU-31 a promising candidate for further preclinical research.

A logical next step for this research could be to employ longitudinal technologies to measure morphofunctional effects at the level of synaptic structures in the neocortex of laboratory animals using confocal microscopy. These technologies would allow for the assessment of the temporal dynamics of both the development of psychosis (under chronic apomorphine administration) and its mitigation (with the administration of benzimidazole derivatives), including the characterization of individual animal responses in the experimental model.

CONCLUSION

In the present study, a comprehensive analysis of benzimidazole derivatives was conducted to search for substances with atypical antipsychotic activity. The use of QSAR modeling and pharmacophore analysis allowed for the identification of the most promising compounds, among which RU-31 demonstrated high affinity for the 5-HT_{2A} receptor and significant antipsychotic activity in *in vivo* experiments. The results showed that RU-31 possesses the characteristics of an atypical antipsychotic with a low risk of extrapyramidal side effects, making it a promising candidate for further study and the development of new drugs for treating psychoses.

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This study did not have financial support from third-party organizations.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Konstantin Yu. Kalitin — statement of key objectives, analysis of scientific and methodical literature, data processing, writing, and editing of the manuscript; Olga Yu. Mukha — data collection and processing, writing, editing and formatting of the manuscript; Viktor B. Voynov — literature review, discussion of results, editing and formatting of the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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AUTHORS

Konstantin Yu. Kalitin — Candidate of Sciences (Medicine), Assistant Professor, Assistant Professor of the Department of Pharmacology and Bioinformatics, senior researcher at the Laboratory of Metabotropic Drugs of the Scientific Center for Innovative Drugs, Volgograd State Medical University; Senior Researcher at the Laboratory of Synaptic Biology (Priority 2030) of the Southern Federal University. ORCID ID: 0000-0002-0079-853X. E-mail: kkonst8@ya.ru

Olga Yu. Mukha — Assistant of the Department of Pharmacology and Bioinformatics, junior researcher at the Laboratory of Metabotropic Drugs of the Scientific Center for Innovative Drugs, Volgograd State Medical University. Researcher at the Laboratory of Metabotropic Drugs, Scientific Center for Innovative Drugs, Volgograd State Medical University. ORCID ID: 0000-0002-0429-905X. E-mail: olay.myha14@gmail.com

Viktor B. Voynov – Doctor of Sciences (Biology), Chief Researcher at the Laboratory of Synaptic Biology (Priority 2030) of the Southern Federal University. ORCID ID: 0000-0002-0242-6270. E-mail: vvoynov@sfedu.ru

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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The efficacy of liraglutide-based drugs on the model of induced metabolic syndrome in experimental animals

A.A. Andreev-Andrievsky[1, 2], M.A. Mashkin[1], M. Wannouss[1], O.V. Fadeeva[3], Yu.G. Kazaishvili[4], D.V. Kurkin[5, 6], K.Ya. Zaslavskaya[7], P.A. Bely[5], A.V. Taganov[8], E.A. Rogozhina[9], K.N. Koryanova[8, 10], E.S. Mishchenko[10], T.G. Bodrova[5], V.S. Shcherbakova[4]

[1] Institute for Biomedical Problems of the Russian Academy of Sciences,
76A Khoroshevskoe Hwy, Moscow, Russia, 123007
[2] Lomonosov Moscow State University,
1 Leninskie Gory, Moscow, Russia, 119991
[3] Research Institute of Mitoengineering of Moscow State University,
2, Leninskiye Gory, bldg.1, Moscow, Russia, 119234
[4] Tver State Medical University,
4 Sovetskaya Str., Tver, Russia, 170100
[5] Russian University of Medicine,
4 Dolgorukovskaya Str., Moscow, Russia, 127006
[6] Volgograd State Medical University
1 Pavshikh Bortsov Sq., Volgograd, Russia, 400066
[7] National Research Ogarev Mordovia State University,
68 Bolshevistskaya Str., Saransk, Russia, 430005
[8] Russian Medical Academy of Continuing Professional Education,
2/1 Barrikadnaya Str., Moscow, Russia, 125993
[9] MIREA, Russian Technological University,
78 Vernadsky Ave., Moscow, Russia, 119454
[10] Pyatigorsk Medical and Pharmaceutical Institute –
branch of Volgograd State Medical University,
11 Kalinin Ave., Pyatigorsk, Russia, 357532

E-mail: victoria_kaptar@mail.ru

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Today, there is an annual increase in the prevalence of obesity and overweight worldwide. This problem is becoming particularly relevant, since these conditions serve as key risk factors for the development of a number of cardiovascular and metabolic disorders, including type 2 diabetes mellitus (T2DM). On the territory of the Russian Federation, drugs were presented as agonists of glucagon-like peptide of the first type (GLP-1) receptors, the active substance of which was produced exclusively by biotechnological means. It is important to note that solid-phase chemical synthesis is also one of the alternative methods for obtaining GLP-1 analogues. A significant advantage of this method over biotechnological synthesis is the exclusion of spontaneous amino acid substitutions and the absence of impurities characteristic of this method.

The aim. Evaluation of the biological activity of the domestic medicinal product liraglutide (Enligria®, solution for subcutaneous administration, 6 mg/ml, PROMOMED RUS LLC), obtained by chemical synthesis, and a foreign reference drug (Saxenda®, solution for subcutaneous administration, 6 mg/ml, NovoNordisk A/C), obtained biotechnologically.

Materials and methods. The effectiveness of liraglutide preparations was evaluated using a model of induced metabolic syndrome in CBA×C57BL/6 SPF mice (*n*=36, age 6 months) according to changes in body weight, feed intake, blood glucose and lipid levels, and adipose tissue mass.

Results. According to the results of the study, it was shown that Enligria® and Saxenda® drugs have comparable efficacy parameters and statistically significantly (p <0.05) reduce body weight (13.6±2.1% and 13.3±3.3%, respectively), glucose levels

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(18±3% and 16±9%), triglycerides (32±12% and 40±18 %) and cholesterol (16±7% and 18±9%) in the blood. Enligria® reduced the mass of structural subcutaneous fat by 32±3% (p <0.0001), and visceral fat by 34±4% (p <0.0001). The studied liraglutide preparations showed a pronounced hypoglycemic effect, observed in all dose ranges. The observed hypoglycemic effect was dose-dependent.

Conclusion. The results of the work indicate the high effectiveness of the synthetic drug Enligria®, which is expressed in reducing body weight and improving metabolic parameters.

Keywords: GLP-1 agonist; liraglutide; peptide; metabolic syndrome; type 2 diabetes mellitus; obesity; weight loss; glucose; lipids; experiment

Abbreviations: GLP-1 — glucagon-like peptide of the first type; DPP-4 — dipeptidyl peptidase 4; BMI — body mass index; BW — body weight; T2DM — type 2 diabetes mellitus; SS — saline solution; EC_{50} — half maximal effective concentration.

Исследование эффективности лекарственных препаратов лираглутида на модели индуцированного метаболического синдрома у экспериментальных животных

А.А. Андреев-Андриевский[1, 2], М.А. Машкин[1], М. Ваннус[1], О.В. Фадеева[3], Ю.Г. Казаишвили[4], Д.В. Куркин[5, 6], К.Я. Заславская[7], П.А. Белый[5], А.В. Таганов[8], Е.А. Рогожина[9], К.Н. Корянова[8, 10], Е.С. Мищенко[10], Т.Г. Бодрова[5], В.С. Щербакова[4]

[1] Федеральное государственное бюджетное учреждение науки
Государственный научный центр Российской Федерации –
Институт медико-биологических проблем Российской академии наук,
Россия, 123007, г. Москва, Хорошевское шоссе, д. 76А
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Московский государственный университет имени М.В. Ломоносова»,
Россия, 119991, г. Москва, Ленинские горы, д. 1
[3] Общество с ограниченной ответственностью
«Научно-исследовательский институт митоинженерии МГУ»
Россия, 119234, г. Москва, тер Ленинские Горы, д. 1 стр. 75-а, эт. 1, пом. II, ком. 17
[4] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Тверской государственный медицинский университет»
Министерства здравоохранения Российской Федерации,
Россия, 170100, г. Тверь, ул. Советская, д. 4
[5] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Российский университет медицины»
Министерства здравоохранения Российской Федерации,
Россия, 127006, г. Москва, ул. Долгоруковская, д. 4
[6] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Волгоградский государственный медицинский университет»
Министерства здравоохранения Российской Федерации,
Россия, 400066, г. Волгоград, пл. Павших Борцов, д. 1
[7] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Национальный исследовательский Мордовский государственный университет имени Н.П. Огарёва»
Россия, 430005, г. Саранск, ул. Большевистская, д. 68
[8] Федеральное государственное бюджетное образовательное учреждение дополнительного
профессионального образования «Российская медицинская академия непрерывного
профессионального образования» Министерства здравоохранения Российской Федерации,
Россия, 125993, г. Москва, ул. Баррикадная, д. 2/1, стр. 1
[9] Федеральное государственное бюджетное образовательное учреждение высшего образования
«МИРЭА – Российский технологический университет»,
Россия, 119454, г. Москва, пр-кт Вернадского, д. 78
[10] Пятигорский медико-фармацевтический институт –
филиал федерального государственного бюджетного образовательного учреждения
высшего образования «Волгоградский государственный медицинский университет»
Министерства здравоохранения Российской Федерации,
Россия, 357532, г. Пятигорск, пр-кт Калинина, д. 11

E-mail: victoria_kaptar@mail.ru

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На сегодняшний день наблюдается ежегодный рост темпов распространенности ожирения и избыточной массы тела во всем мире. Данная проблема приобретает особую актуальность, поскольку эти состояния служат ключевыми факторами риска развития целого ряда сердечно-сосудистых и метаболических нарушений, включая сахарный

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диабет 2 типа (СД2). На территории РФ в качестве агонистов рецепторов глюкагоноподобного пептида первого типа (ГПП-1) были представлены препараты, действующее вещество которых производилось исключительно биотехнологическим путём. Важно отметить, что так же одним из альтернативных способов получения аналогов ГПП-1 является твердофазный химический синтез. Существенным преимуществом данного метода перед биотехнологическим синтезом является исключение спонтанных замен аминокислот и отсутствие характерных для химического метода синтеза примесей.

Цель. Оценить биологическую активность российского лекарственного препарата лираглутида (Энлигрия®, раствор для подкожного введения, 6 мг/мл, ООО «ПРОМОМЕД РУС»), полученного методом химического синтеза, и зарубежного референтного препарата (Саксенда®, раствор для подкожного введения, 6 мг/мл, НовоНордиск А/С), полученного биотехнологическим путём.

Материалы и методы. Эффективность препаратов лираглутида оценивали на модели индуцированного метаболического синдрома у мышей CBA×C57BL/6 SPF-категории (n=36, возраст 6 мес.) по изменению показателей массы тела, потребления корма, уровня глюкозы и липидов в крови, а также массы жировой ткани.

Результаты. По результатам проведённого исследования было показано, что препараты Энлигрия® и Саксенда® имеют сопоставимые параметры эффективности и статистически значимо (p <0,05) снижают массу тела (13,6±2,1 и 13,3±3,3%, соответственно), уровень глюкозы (18±3 и 16±9%), триглицеридов (32±12 и 40±18%) и холестерина (16±7 и 18±9%) в крови. Препарат Энлигрия® снижал массу структурного подкожного жира на 32±3% (p <0,0001), а висцерального жира на 34±4% (p <0,0001). Исследуемые препараты лираглутида показали выраженное гипогликемическое действие, наблюдавшееся во всех диапазонах исследуемых доз. Наблюдаемый гипогликемический эффект носил дозозависимый характер.

Заключение. Результаты работы свидетельствуют о высокой эффективности синтетического препарата Энлигрия®, выраженной в снижении массы тела и улучшении метаболических параметров.

Ключевые слова: агонист ГПП-1; лираглутид; пептид; метаболический синдром; сахарный диабет 2 типа; ожирение; снижение массы тела; глюкоза; липиды; эксперимент

Список сокращений: ГПП-1 — глюкагоноподобный пептид первого типа; ДПП-4 — дипептидилпептидаза 4; ИМТ — индекс массы тела; МТ — масса тела; СД2 — сахарный диабет второго типа; ФР — физиологический раствор; EC_{50} — полуэффективная концентрация.

INTRODUCTION

Obesity is one of the most important health problems. According to the WHO, there are currently more than 1.6 billion people over 15 years of age with excess body weight (body mass index [BMI] = 25.0–29.0 kg/m^2) and more than 400 million people suffering from obesity (BMI > 30 kg/m^2) [1–3]. An epidemiological link has been established between excess body weight and type 2 diabetes mellitus (T2DM): over 75% of cases are associated with excess body weight and obesity. More than 50% of patients with T2DM have a BMI > 30 kg/m^2 [1, 3]. It is important to note that people with excess body weight and obesity are also significantly more likely to be diagnosed with hypertension (34–64%), gallbladder disease (35–45%) and osteoarthritis (5–17%) [4].

Over the past decade, the possibilities for treating obesity and T2DM have significantly expanded due to the emergence of a new class of medicines — glucagon-like peptide-1 (GLP-1) receptor agonists. Previously, medicines with active ingredient produced exclusively by biotechnological means were presented on the pharmacy market as GLP-1 receptor agonists [5]. However, the disadvantages of biotechnological production, including the need to ensure the genetic stability of producer strains and the potential risk of developing adverse reactions of immune system, demonstrated the need to study and develop alternative methods for producing GLP-1 receptor agonists. One of the alternative methods for producing GLP-1 analogs is chemical synthesis [1, 4, 6]. Modern automated directed synthesis systems allow to obtain linear peptides up to 100 amino acids long. A significant advantage of this method is the exclusion of spontaneous substitutions of the amino acid sequence, typical for biotechnological synthesis, and the purity of the product (there are no impurities of residual nucleic acids and producer proteins), which eliminates the risk of immunogenicity while maintaining effectiveness, and also ensures a high safety profile of the drug[1] [7–9].

Until recently, only foreign drugs from the group of GLP-1 receptor agonists were registered in the Russian Federation: Saxenda® (INN: liraglutide), Victoza® (INN: liraglutide) and Ozempic® (INN: semaglutide), which are products of Novo Nordisk A/S (Denmark). In September 2023, the Russian company PROMOMED RUS registered the first liraglutide drug — Enligria®, a solution for subcutaneous administration, 6 mg/mL, registration certificate No. LP-008822, the active ingredient of which is obtained synthetically. Figure 1 shows the structure of liraglutide.

[1] FDA. ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry. Guidance for Industry. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/andas-certain-highly-purified-synthetic-peptide-drug-products-refer-listed-drugs-rdna-origin

THE AIM. To evaluate comparative efficacy of the Russian liraglutide medicine (chemical synthesis) and the foreign reference medicine (biotechnological synthesis).

MATERIALS AND METHODS

Test system

The study was conducted using the automated Phenomaster platform (TSE Instruments, Germany) to obtain a statistically significant effect in a biological experiment in accordance with the Guidelines for Preclinical studies[2]. The work used 36 male CBA×C57BL/6 mice aged 6 months of SPF category produced by the Center for Genetic Resources of Laboratory Animals of the ICiG SB RAS. The duration of adaptation after receipt from the nursery was more than 14 days. Mice were kept in groups of 2 in individually ventilated GM500 cages (Tecniplast, Italy) with a floor area of 500 cm^2 and a height of 16 cm. Wood chips of deciduous species (fraction 3, IP Filonich, Russia) were used as bedding. Cages were changed at least every 3 weeks. The temperature in the animal housing facilities ranged from 20 to 24°C, relative humidity — from 30 to 70%. Light mode is direct, 12-hour, light on at 09 a.m. To enrich the habitat, the animals were given nesting material and cardboard shelters. Materials entering the animals were sterilized by autoclaving.

The experiment used a diet-induced model of metabolic syndrome in mice [6, 9, 10]. Animals received a high-calorie diet (35% P-22 feed [Bio-Pro, Russia], 35% condensed milk, 30% melted beef fat) and 30% fructose syrup for at least 3 months. By the start of the study, the mice had a BMI of 45–50 g and a pronounced metabolic syndrome, confirmed by a glucose tolerance test. The animals were divided into 3 experimental groups of 12 individuals each.

Ethics approval

The study design and animal housing conditions were selected in accordance with the Guidelines of the EEC No. 33 dated November 14, 2023. Throughout the study, the animals had unlimited access to food and purified water. A Bioethical approval of the study plan was carried out by the Commission on Bioethics of the Institute of Biomedical Problems of the Russian Academy of Sciences (Protocol No. 648 dated September 28, 2023). When handling animals, the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) were observed.

Design of experiment

Distribution into experimental groups

Mice were distributed into experimental groups by randomization using GraphPad Prizm v. 8 Software. The cage was used as an element of randomization.

Dosage regimen

The study drug and saline solution (SS) were administered subcutaneously, into the withers, 1 time/day, starting from day 1 of the experiment. Administration was carried out using 0.5 mL injection syringes with G29 needles (5 mL/kg total).

Due to the fact that subcutaneous injections, themselves, are a source of stress for animals, the animals were accustomed to manipulations for 1 week of the experiment. To do this, 5 ml/kg of SS was administered subcutaneously daily. Then, the mice in the experimental group began to be injected with the studied liraglutide (Enligria®, solution for subcutaneous administration, 6 mg/mL, PROMOMED RUS LLC, Russia), the mice in the comparison group — with a commercially available liraglutide drug (Saxenda®, solution for subcutaneous administration, 6 mg/mL, Novo Nordisk A/S, Denmark), and the mice in the control group continued to be injected with SS. The doses of liraglutide were sequentially increased, starting from the first test dose — 0.1 mg/kg. The criterion for increasing the dose was the absence of changes in the body weight (BW) of mice by more than 2% in 3 days. Liraglutide and SS were administered subcutaneously 1 time/day in the evening (before the daily peak of feed consumption). The duration of administration of substances was 21 days.

Duration of the study

The experiment was conducted from Augst 10, 2023 to September 05, 2023.

The duration of administration of substances was 21 days. In total, mice received 4 injections of 0.1 mg/kg, 9 injections of 0.2 mg/kg, 4 injections of 0.4 mg/kg and 5 injections of 0.8 mg/kg in 22 days. In total, mice received 7.8 mg/kg of liraglutide.

[2] Guidelines for conducting preclinical studies of medicines. Part one. Moscow: Grif and K; 2012. 944 p. EDN: SDEWMP. Russian

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In vivo study

The BW of mice was measured daily, starting from the first day of the experiment, with an accuracy of ±0.1 g using ViBRA AJ-2200CE (Japan). The consumption of food and water in the holding cages was carried out daily, starting from the first day of the experiment, by the difference in the mass of the feed/water issued and their residues on the next day (24 ± 2 h). The mass of food and drinks was determined with an accuracy of ±0.1 g using CO 2200 scales (Vibra, Japan). Blood glucose (not fasting) was measured before the start of substance administration and at each dose change using a OneTouch Verio Reflect portable glucometer (LifeScan, Switzerland) and test strips for it according to the manufacturer's instructions. Blood for measurement in a volume of 3–5 µL was obtained by puncture of the tip of the tail.

Euthanasia

Euthanasia of mice was performed by inhalation of isoflurane followed by exsanguination. Mice were placed in a priming chamber for induction anesthesia (isoflurane 5%). After loss of posture and slowing of breathing, without stopping isoflurane inhalation using a mask, the chest was opened in the mice and the maximum possible volume of blood (≈1 mL) was taken from the right ventricle using a 2 ml injection syringe. At the end of the procedure, to guarantee the death of the animal, the heart was cut off from the main vessels.

Collection and handling of blood samples

The collected blood was placed in microcentrifuge tubes with a clot activator and separation gel. After clotting, but no later than 2 h after blood collection, the serum was separated by centrifugation at 2500 g and room temperature for 15 min. The serum was decanted into labeled 1.5 ml microcentrifuge tubes, frozen and stored at a temperature not higher than minus 18°C until analysis, but no longer than 1 month.

Necropsy

During necropsy, a visual assessment of fat depots was performed and internal organs were excised to determine their BW.

Visual assessment of fat depots: subcutaneous fat depots (interscapular, anterior subcutaneous, brachial, inguinal and popliteal) and visceral (mesenteric, perirenal, pericardial, gonadal) were examined. Each depot was evaluated in points according to the following scale: 0 — not expressed (adipose tissue is practically absent); 1 — moderately expressed; 2 — well expressed (there is a lot of adipose tissue). The total score for the animal was calculated as the sum of the scores for all fat depots.

During necropsy, the following organs were excised and weighed (±1 mg, Vibra ALE323R scales, Japan): visceral fat, brain, thymus, heart, lungs, spleen, pancreas, liver, kidney, adrenal glands, testicles, epididymides, accessory apparatus (prostate and seminal vesicles complex), triceps muscle of the lower leg.

Biochemical blood test

The concentration of glucose, triglycerides and cholesterol was analyzed in the serum. The analysis was performed on an automatic analyzer A25 (Biosystems, Spain) using Hospitex Diagnostics reagent kits and control materials (Italy) according to the reagent manufacturer's instructions.

Statistical processing

Dose-effect curves were analyzed by nonlinear regression. MS Excel Software (v. 16.82, Microsoft Corp., USA) and Prism (v. 10.2, GraphPad, USA) were used for data analysis. Data are presented as mean arithmetic and standard deviation (M ± SD). Statistical data analysis was performed using one-way (factor "group") and two-way (factors "group" and "time") analysis of variance with subsequent pairwise comparisons using the Sidak or Tukey test. Differences were considered significant at $p < 0.05$.

RESULTS

Change in body weight

Data on the BW of mice are presented in Figure 2. Getting used to the subcutaneous injection procedure was accompanied by some decrease in BW (-6.4 ± 0.3%). After 4 days of administration, the BW stabilized. Then, the animals of the experimental groups began to be injected with medicine T (study) or R (compared medicine), and the mice of the control group continued to be injected with SS. The administration of liraglutide led to a progressive decrease in the BW of mice in the experimental groups (T and R), while the BW of mice in the control group did not change significantly. Differences in the BW of mice in the control and experimental groups reached the level of statistical significance from day 4 of drug administration ($p < 0.05$). The maximum decrease in BW was 13.6 ± 2.1 and 13.3 ± 3.3% for T and R, respectively.

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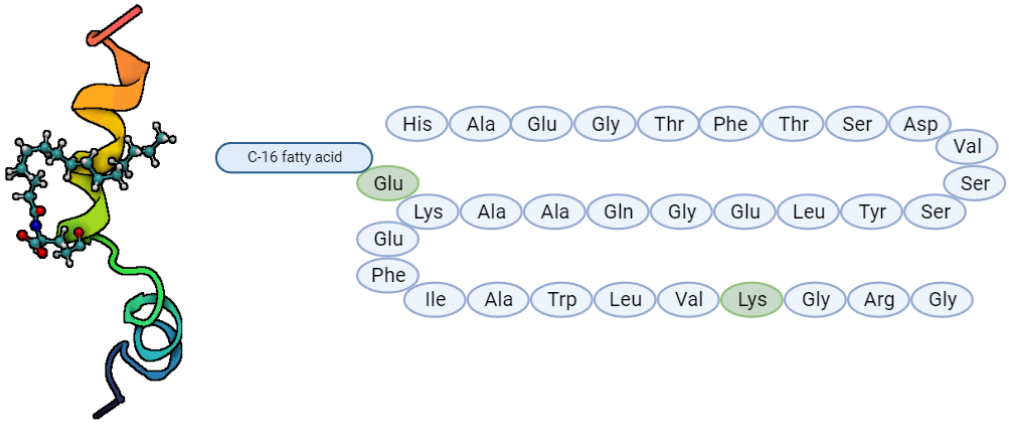

Figure 1 – Structure of liraglutide

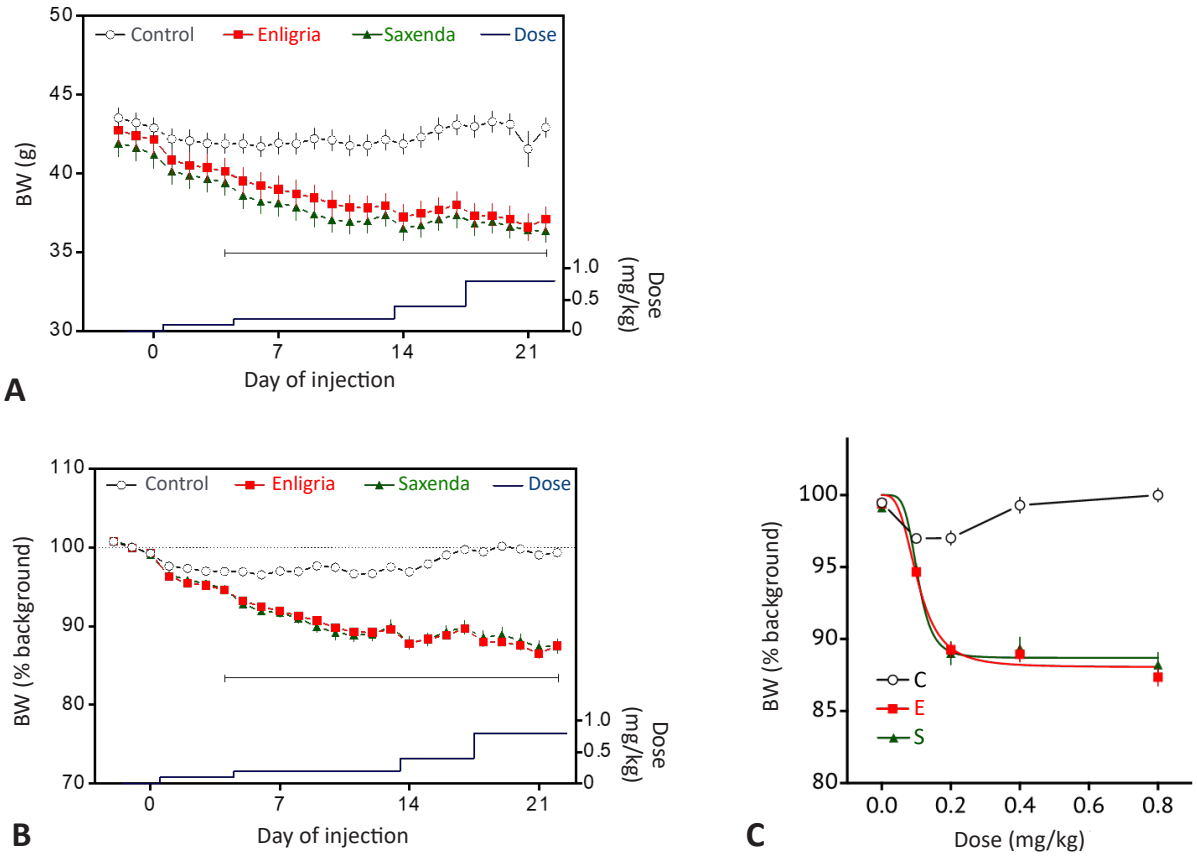

Figure 2 – Change in body weight of animals

Note: A — change in absolute body weight; B — change relative to body weight (expressed in relation to background values, before the start of substance administration, during the habituation of animals to subcutaneous injections); C — dependence of body weight on the dose of administered drugs. BW — body weight.

Table 1 – Data of variance analysis and subsequent pairwise comparisons of body weight change

Factor	df1	df2	F-value	*p*-value
Term × Group (Interaction)	48	792	52.70	< 0.0001
Term (Time)	24	792	218.4	< 0.0001
Group	2	33	81.47	< 0.0001

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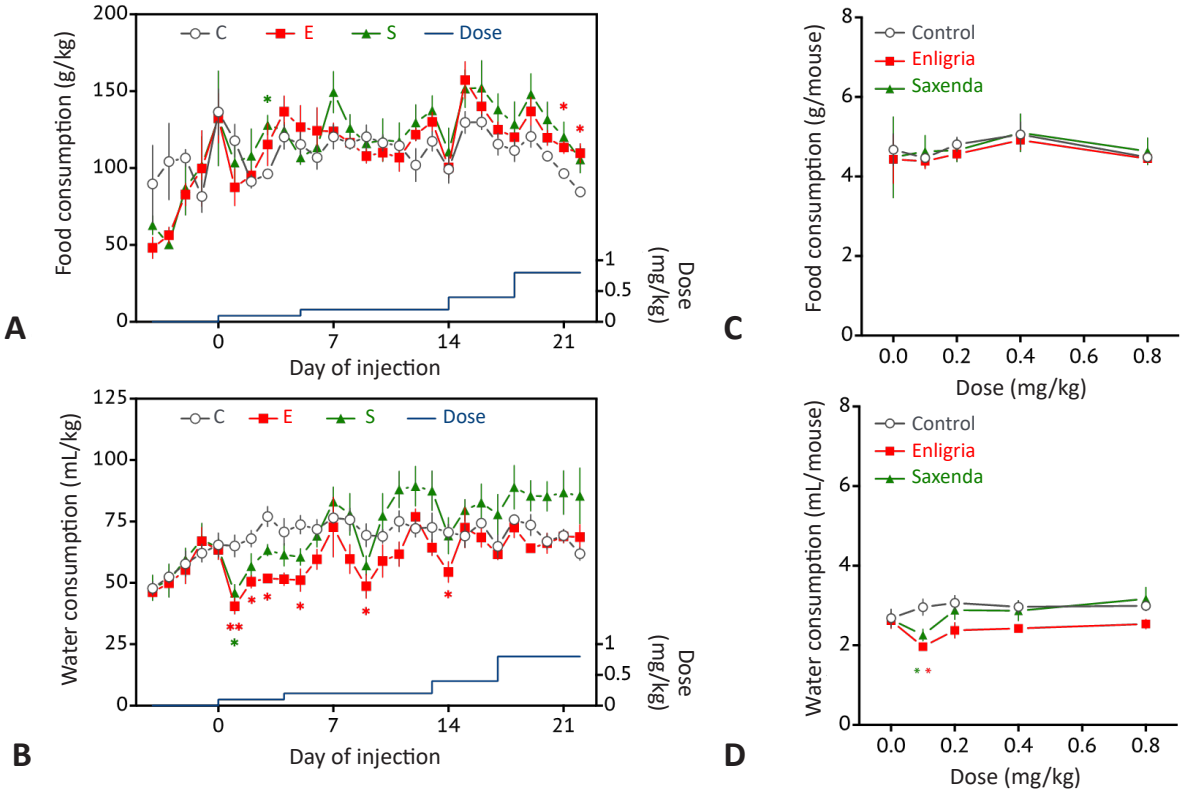

Figure 3 – Change in the amount of food and water consumption by animals

Note: Feed (A) and water (B) consumption depending on and the time of the study. Dependence of feed (C) and water (D) consumption the dose of the administered drug. * — $p < 0.05$, ** — $p < 0.01$ (Tukey test). E — Enligria®; S — Saxenda®; C — control.

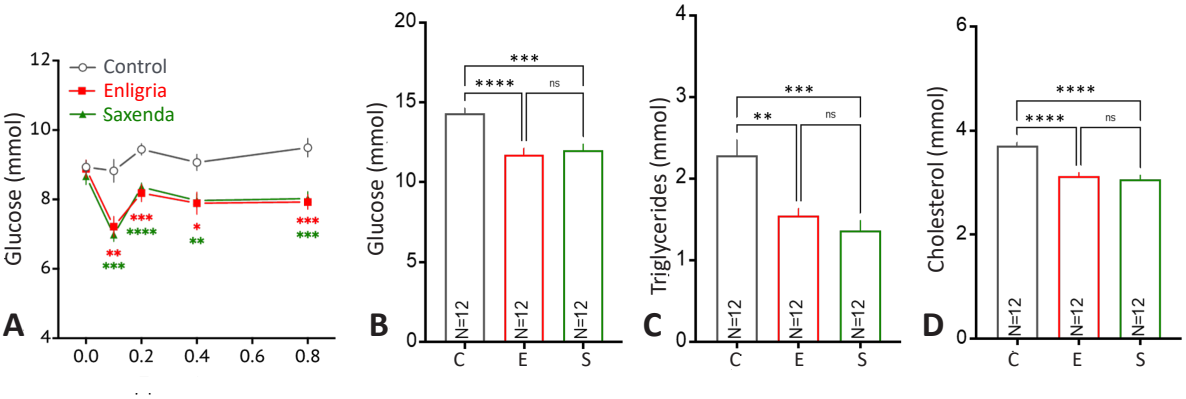

Figure 4 – Dynamics of changes in blood parameters in animals

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant (Tukey test).

Table 2 – Data of variance analysis and subsequent pairwise comparisons of changes in water and food consumption

Data block	df1	df2	F	*p*-value
Food consumption — dynamics over time, intergroup analysis	2	9	0.50	0.6224
Food consumption — dose dependence, intergroup analysis	2	9	0.08	0.9219
Water consumption — dynamics over time, intergroup analysis	2	9	2.94	0.1041
Water consumption — dose dependence, intergroup analysis	2	9	2.97	0.1021

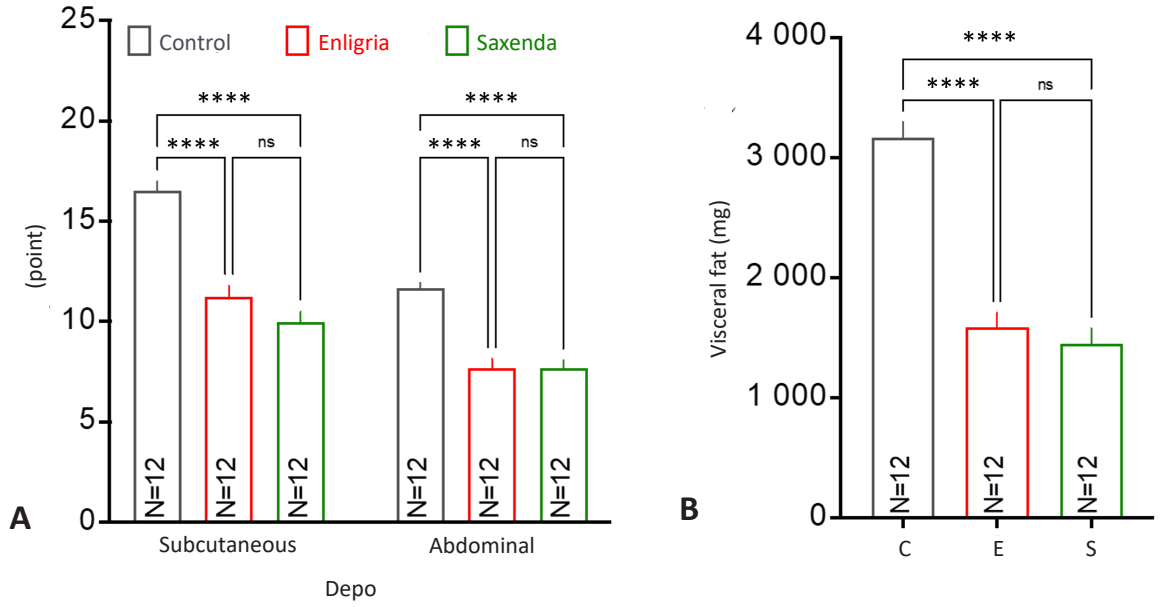

Figure 5 – Severity of fat depots according to visual assessment data (A) and visceral fat mass (B)
Note: **** — p <0.0001, ns — not significant (Tukey test).

Table 3 – Indicators of the mass of internal organs of mice (in mg) receiving liraglutide drugs 0.1–0.8 mg/kg or saline

Organ / tissue	Control	Enligria	Saxenda	Statistical data
Brain	496 ± 3	490 ± 2	491 ± 4	$F_{(2, 33)}$ = 0.94; p = 0.4019
Heart	173 ± 3	149 ± 4**** (-14 ± 2 %)	151 ± 3*** (-13 ± 2 %)	$F_{(2, 33)}$ = 15.43; p < 0.0001
Lungs	171 ± 4	169 ± 4	167 ± 3	$F_{(2, 33)}$ = 0.26; p = 0.7758
Kidneys	274 ± 6	256 ± 6	263 ± 4	$F_{(2, 33)}$ = 2.65; p = 0.0855
Liver	1890 ± 61	1565 ± 52*** (-17 ± 3%)	1469 ± 54**** (-22 ± 3%)	$F_{(2, 33)}$ = 15.72; p < 0.0001
Pancreas	239 ± 6	262 ± 10	261 ± 9	$F_{(2, 33)}$ = 2.13; p = 0.1347
Spleen	78,8 ± 1,6	72,8 ± 1,3* (-8 ± 2%)	71,6 ± 1,9** (-9 ± 2%)	$F_{(2, 33)}$ = 5.69; p = 0.0076
Triceps muscle of the lower leg	223 ± 3	211 ± 3* (-6 ± 1%)	206 ± 4** (-8 ± 2%)	$F_{(2, 33)}$ = 6.19, p = 0.0052
Testicle	113 ± 1	116 ± 2	115 ± 2	$F_{(2, 33)}$ = 0.89; p = 0.4207

Note: * — p <0.05; ** — p <0.01; *** — p <0.001; **** — p <0.0001, ns — not significant (Tukey test). For significant differences, the value of the change in organ mass in percent relative to the control group is given in parentheses. Data are presented as M±SD.

To analyze the dependence of the effect of medicines on the BW of mice on the dose, half maximal effective concentrations — EC_{50} were calculated (Fig. 2B). The half maximal effective concentration for the study drug was 0.179 mg/kg (95% CI = 0.152–0.235), for the comparison drug — 0.156 mg/kg (95% CI = 0.123–0.208). The EC_{50} values for the two medicines did not differ significantly ($F_{(1, 114)}$ = 0.92, p = 0.3406). Dose-effect curves were satisfactorily ($R^2 \approx 0.8$) described by a 4-parameter logistic function. Table 1 presents the data of statistical analysis.

Food and water consumption

The amount of food and water consumed by animals in the experimental groups did not differ significantly (Table 2). During the experiment, at the initial stage of drug administration, a decrease in water consumption was noted in the groups of animals receiving liraglutide, which was established in almost all toxicological and pharmacological studies (OECD 407/408/409, ICH M3[R2]). The fact that during the experiment the amount of water consumed by the control and experimental groups had similar values indicates the absence of a systemic effect.

The difference in BW changes between the comparison and control groups during the experiment was also not observed (Fig. 3). Table 2 presents the data of statistical analysis.

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Blood parameters

The concentration of glucose in the blood (not fasting) decreased after the start of administration of liraglutide, while the severity of the decrease did not depend on the study drug and dose (Fig. 4A). The concentration of glucose in the blood of mice receiving drugs T and R was reduced compared to mice in the control group by 18 ± 3% ($p < 0.0001$) and 16 ± 9% ($p < 0.001$), respectively. The concentrations of triglycerides in mice receiving drugs T and R decreased by the end of the experiment by 32±13% (p <0.01) and 33±18% (p <0.001), respectively (Fig. 4 B, C). When the study drugs were administered, a decrease in cholesterol concentration relative to the control group was observed ($p < 0.0001$). Thus, for the liraglutide drug (T), this indicator was 17.7 ± 6.8%, for R — 16.6 ± 8.6% (Fig. 2D). Biochemical blood parameters of mice receiving liraglutide drugs did not differ between themselves.

Assessment of the amount of adipose tissue

The severity of the decrease in the amount of adipose tissue in mice receiving liraglutide was indistinguishable both according to visual assessment data and according to indicators of visceral fat mass.

The severity of subcutaneous and visceral fat depots during visual assessment significantly decreased in animals receiving drugs T and R (Fig. 5A). Thus, in mice receiving the study drug, subcutaneous fat depots were 32 ± 3% ($p < 0.0001$), visceral fat depots were 34 ± 4% ($p < 0.0001$) less pronounced than in control individuals. In animals receiving the reference drug, these values decreased, respectively, by 39 ± 3% ($p < 0.0001$) and 34 ± 4% ($p < 0.0001$) than in mice that were injected with SS.

During necropsy, visceral fat (epididymal, perirenal) was excised from mice and its mass was determined. The mass of adipose tissue in mice receiving liraglutide drugs was sharply reduced compared to control individuals (Fig. 5 B). In mice that were injected with the study drug, the decrease in adipose tissue mass was 50 ± 14% ($p < 0.0001$), in animals receiving the reference drug — 54 ± 14% ($p < 0.0001$).

Mass of internal organs

During necropsy, the main organs and tissues were excised and examined. Given the significant differences in the mass of animals, as well as the fact that the mass of most internal organs are allometrically proportional to lean (without adipose tissue), and not total BW. Data on absolute mass, and not mass coefficients, were used to analyze the mass of internal organs. The mass of the brain, lungs, pancreas, testicles, adrenal glands in mice receiving liraglutide preparations did not differ from the values of the control group, which indicates the safety of therapy (Table 3). The mass of the liver, heart, spleen and triceps muscle of the lower leg in groups of animals receiving medicines T and R were less than in control individuals, which indicates a positive effect of the medicine in relation to reducing the amount of visceral fat associated with the development of complications.

DISCUSSION

GLP-1 is one of the most important and studied incretin hormones responsible for glucose homeostasis when it enters the body with food [10–12]. It has been established that up to 70% of glucose-dependent insulin secretion is due to the incretin effect. Normally, endogenous GLP-1s are synthesized in the L-cells of the intestine in response to food intake.

It is known that in T2DM, the incretin effect is reduced, which determines the therapeutic potential of hypoglycemic agents that restore the incretin effect [1]. It is important to note that GLP-1 produced by intestinal cells activates receptors located on sensory neurons of the *vagus* nerve, thereby regulating the activity of various areas of the brain. In addition, GLP-1 receptors are expressed in different areas of the brain, where GLP-1 behaves as a neuropeptide involved in various specific effects, including appetite control, water consumption and stress response [3].

In clinical studies in patients with T2DM, the beneficial effects of native GLP-1 were limited by a short half-life, which is approximately 2–5 min, due to their degradation by the enzyme dipeptidyl peptidase 4 (DPP-4). To reduce the effect of the enzyme, DPP-4-resistant GLP-1 agonists conjugated with a lipid, such as liraglutide, have been developed [7, 10–13]. Liraglutide is a peptide 97% homologous to the native hormone in terms of amino acid composition, and modified with a 16-carbon fatty acid residue by attaching it through a glutamic spacer to the ε-amino group of lysine (ε-Lys26). This structure provides protection against DPP-4, and, as a result, prolongs activity [14, 15].

In this *in vivo* study, the efficacy of the Russian liraglutide drug (Enligria®), the active ingredient of which is obtained by chemical synthesis, and a commercially available foreign analogue (Saxenda®), the active ingredient of which is obtained by biotechnological synthesis, was studied.

The results of the study showed that mice with excess BW receiving liraglutide had a pronounced decrease in BW compared to the control group. The decrease in the level of adipose tissue was statistically significant, with comparable results for both the original and the Russian drug. Blood glucose levels also decreased, indicating improved glycemic control. In addition, triglyceride and total cholesterol levels in the blood showed a noticeable decrease. These study data confirm the efficacy of liraglutide both in the original and in the Russian version in the context of treating excess BW and metabolic disorders. Since the severity of the effect was similar for both forms of medicines, this may indicate the high quality of the Russian analogue, which is an important aspect for clinical use in practice. Comparison of half maximal effective doses indicates identical mechanisms of action and equivalent bioavailability of both drugs.

In contrast to the appetite suppression in humans well described in the work of C. Verdich et al. for liraglutide, in our in vivo work, suppression of feed consumption was not observed, which is probably based on species differences between mice and the human body [16]. It has previously been shown that one of the leading mechanisms mediating the decrease in BW in mice when GLP-1 receptors are activated is stimulation of the sympathetic nervous system [17, 18] and β3-adrenoreceptor-mediated decrease in fat deposition by white adipose tissue adipocytes [2, 19], as well as induction of thermogenic expression, “browning” of adipose tissue [14, 20]. These observations are in good agreement with our data on a significant decrease in the mass of fat depots in animals receiving liraglutide preparations. It is important that the central effects of GLP-1 agonists on adipocyte metabolism were manifested with a normal diet [19, 21].

A pronounced hypoglycemic effect was found for the studied drugs, which was observed even at the smallest of the doses we studied — 0.1 mg/kg. Increasing the dose of liraglutide was not accompanied by an increase in the hypoglycemic effect. It can be assumed that already 0.1 mg/kg of the peptide was a saturating concentration for peripheral (in the pancreas) GLP-1 receptors, while the lower bioavailability of liraglutide for central receptors due to low penetration through the blood-brain barrier [22, 23] led to a gradual increase in the central action of liraglutides with increasing dose and a progressive decrease in BW.

When examining the internal organs of mice on day 21 of administration of liraglutide preparations, a significant decrease in liver mass was found. The liver of obese mice contains at least ≈10% fat (up to 30%) [24, 25]. Given the data on the enhancement of β-oxidation of fatty acids in a number of tissues when peripheral GLP-1 receptors are activated, it can be assumed that the decrease in liver mass was due to a decrease in fat content [12, 26]. The data obtained also confirm the high potential of GLP-1 agonists in the treatment of non-alcoholic fatty liver disease. Muscles contain significantly less adipose tissue, which is in good agreement with the less pronounced decrease in the mass of the triceps muscle of the lower leg we studied in animals receiving liraglutides. In this regard, it should be noted that GLP-1 receptor agonists prevent the loss of muscle mass by suppressing the expression of ubiquitin ligases and stimulating the differentiation of muscle cells [27].

For all the studied organs and tissues, there were no differences in the effects of liraglutide drugs obtained by biotechnological and synthetic methods of synthesis.

As a result of our previous studies, a sufficient amount of data has been collected confirming the similarity of the physicochemical and biological properties of these drugs [2]. Verification of the amino acid sequence of peptides in both drugs and determination of the intact mass were carried out by liquid chromatography mass spectrometry (LC-MS). The similarity of the profiles of the active substance, high-molecular compounds and related impurities contained in the drugs was confirmed by reversed-phase and size-exclusion HPLC techniques. At the same time, the content of impurities in liraglutide obtained by chemical synthesis was 3.5 times lower than in the original medicine, which confirms the advantages of the chosen technology for the production of the substance [2]. The comparability of the biological activity of the drugs was confirmed in in vitro studies on the CHO-K1 / GLP-1R cell type (GenScript, USA) [2]. In the conducted bioequivalence study, no adverse events were observed, and the tolerability of the test drugs was assessed as “good”. At the same time, it is important to note that no cases of immunogenicity were noted for the Russian drug, which confirms the reduction in the risk of lack of effectiveness of therapy and the high safety profile of the drug [2].

Thus, as a result of the studies carried out, it can be concluded that the drug Enligria® (INN: liraglutide), solution for subcutaneous administration, 6 mg/mL,

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PROMOMED RUS LLC, and Saxenda® (INN: liraglutide), solution for subcutaneous administration, 6 mg/mL, Novo Nordisk A/S, are bioequivalent.

Limitations of the study

Despite the fact that the use of an experimental model on CBA×C57BL/6 mice to study metabolic syndrome can provide valuable data, it is also important to be aware of the limitations that may affect the validity and generalizability of the results. For example, C57BL/6 mice are known to have a high risk of developing obesity and insulin resistance on a high-fat diet, which may not reflect the reactions of other animal strains [28]. This fact may lead to the fact that the results will not be applicable to a wider population of mammals, including humans. It is also important to consider possible combinations of diet and habitat that may affect the behavior and physiology of animals. For example, the presence of stressors, such as social interaction or housing conditions, can significantly affect the results, especially in studies related to metabolic disorders and obesity [29]. Finally, it should be noted that differences in methods for measuring fat mass, food consumption, and other biochemical parameters can affect the comparability of data. For example, differences in the biomarkers used to assess glucose and lipid levels can lead to differences in the interpretation of the data obtained [30].

Further studies using diverse models and increasing the sample size may help in a more accurate understanding of the mechanisms and effect of therapy.

CONCLUSION

A comparative study of the efficacy of liraglutide drugs obtained by biotechnological synthesis and by directed peptide synthesis showed the equivalence of their biological activity and safety. This study confirmed the efficacy of liraglutide both in the original and in the Russian version in the context of treating excess BW and metabolic disorders. Since the severity of the effect was similar for both forms of medicines, this may indicate the high quality of the Russian analogue, which is an important aspect for the clinical use of the drug. Comparison of half maximal effective doses indicates identical mechanisms of action and equivalent bioavailability for both drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Alexander A. Andreev-Andrievskiy — development of the preclinical research concept, analysis and description of the results, draft editing; Kira Ya. Zaslavskaya — analysis and selection of literary sources, writing the text of the article; Olga V. Fadeeva — discussion of the design and results of the study; Petr A. Bely — research design implementation, research data processing; Victoria S. Scherbakova, Ekaterina A. Rogozhina — discussion of the design and results of the study; Tatiana G. Bodrova — design development and research concepts; Denis V. Kurkin, Ksenia N. Koryanova, Ekaterina S. Mishchenko — writing and editing the text of an article; Yuri G. Kazaishvili — development of the design and concept of preclinical research; Alexey V. Taganov — search and analysis of literary sources; Majed Wannouss — analysis and description of the results; Mihail A. Mashkin – selection of literary sources, writing the text of the article. All the authors confirm their authorship compliance with the ICMJE international criteria (all the authors made a significant contribution to the conceptualization, conduct of the study and preparation of the article, read and approved the final version before publication).

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AUTHORS

Alexander A. Andreev-Andrievskiy — Candidate of Sciences (Biology), Leading Researcher, Head of Animal Phenotyping Laboratory, Institute for Biomedical Problems of the Russian Academy of Sciences; Senior Researcher, Laboratory of General Physiology and Regulatory Peptides of the Lomonosov Moscow State University. ORCID ID: 0000-0002-1173-8153. E-mail: aaa@imbp.ru

Mihail A. Mashkin — researcher Fellow of Animal Phenotyping Laboratory, Institute for Biomedical Problems of the Russian Academy of Sciences. ORCID ID: 0000-0002-0612-5467. E-mail: mashkin.mikhail.alexandrovich@yandex.ru

Mohammad Vannous — junior researcher of the Laboratory of Animal Phenotyping, Institute for Biomedical Problems of the Russian Academy of Sciences. 0009-0003-5932-0498. E-mail: dr.vannous@gmail.com

Olga V. Fadeeva — Laboratory Research Assistant, Animal Research Department, LLC Research Institute of Mitoengineering of Moscow State University. ORCID ID: 0000-0001-6833-8313. E-mail: ofadeeva@mitotech.ru

Yuri G. Kazaishvili — Candidate of Sciences (Biology), Assistant Professor of the Department of Pharmacology, Tver State Medical University. ORCID ID: 0000-0003-0826-4177. E-mail: ykaza87@icloud.com

Denis V. Kurkin — Doctor of Sciences (Pharmacy), Assistant Professor, Director of the Scientific and Educational Institute of Pharmacy n.a. K.M. Lakin, Russian University of Medicine; Professor of the Department of Clinical Pharmacology and Intensive Care of the Volgograd State Medical University. ORCID ID: 0000-0002-1116-3425. E-mail: strannik986@mail.ru

Kira Ya. Zaslavskaya — Assistant of the Department of Biological and Pharmaceutical Chemistry with the course of organization and management of pharmacy of the National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-7348-9412. E-mail: kiryonok@yandex.ru

Petr A. Bely — Doctor of Sciences (Medicine), Senior Laboratory Assistant of Department of Internal Medicine and Gastroenterology of the Russian University of Medicine. ORCID ID: 0000-0001-5998-4874. E-mail: pbely@ncpharm.ru

Alexey V. Taganov — Doctor of Sciences (Medicine), Professor, Professor of the Department of Infectious Diseases of Russian Medical Academy of Continuous Professional Education. ORCID ID: 0000-0001-5056-374X. E-mail: matis87177@yandex.ru

Ekaterina A. Rogozhina — PhD candidate of the Department of Biotechnology and Industrial Pharmacy of MIREA, Russian Technological University. ORCID ID: 0000-0002-3325-2605. E-mail: e.kate.rogozhina@gmail.com

Ksenia N. Koryanova — Candidate of Sciences (Pharmacy), Assistant Professor of the Department of Pharmacy, Faculty of Postgraduate Education of the Pyatigorsk Medical and Pharmaceutical Institute — branch of Volgograd State Medical University; Assistant Professor of the Department of Pharmacy, General Pharmacology and Pharmaceutical Consulting of the Russian Medical Academy of Continuing Professional Education. ORCID ID: 0000-0003-1571-9301. E-mail: kskor-16@mail.ru

Ekaterina S. Mishchenko — Candidate of Sciences (Pharmacy), Assistant Professor of the Department of Toxicological and Analytical Chemistry, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0001-7778-8391. E-mail: ekaterina-mischenko1809@mail.ru

Tatiana G. Bodrova — PhD candidate of the Scientific and Educational Institute of Pharmacy n.a. K.M. Lakin, Russian University of Medicine. ORCID ID: 0009-0001-0881-4880. E-mail: btatg@mail.ru

Victoria S. Scherbakova – Candidate of Sciences (Biology), Assistant Professor of the Department of Pharmacology, Tver State Medical University. ORCID: 0000-0002-7251-8744. E-mail: victoria_kaptar@mail.ru

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Clinical and economic benefits of using sonidegib in the 1-line therapy of patients with locally advanced basal cell carcinoma

O.I. Ivakhnenko[1], V.V. Ryazhenov[1], M.Yu. Frolov[2], V.A. Rogov[2]

[1] Sechenov First Moscow State Medical University (Sechenov University),
2 Trubetskaya Str., Bldg 8, Moscow, Russia, 119991
[2] Volgograd State Medical University,
1 Pavshikh Bortsov Sq., Volgograd, Russia, 400066

E-mail: oii@hta-expert.ru

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One of the key factors in ensuring the availability of modern treatments and choosing the optimal therapy for patients is the clinical and economic characteristics of new medical technologies.

The aim: to assess the clinical and economic feasibility of using sonidegib in widespread clinical practice.

Materials and methods. General scientific research methods were used as a methodological basis. A "decision tree" model was developed to conduct a clinical and economic assessment. The clinical and economic assessment of the use of sonidegib was carried out from the perspective of the healthcare system of the Russian Federation: the costs of systemic drug therapy for the 1-line of patients with locally advanced basal cell carcinoma (laBCC) were taken into account.

Results. A comparative analysis of efficacy based on the progression-free survival (PFS) criterion revealed the advantage of sonidegib over vismodegib: the odds ratio (OR) of disease progression in patients with laBCC 12 months after the start of therapy was 0.27778 (95% CI 0.125–0.618; p=0.0017; Z=3.1423). The reduction in the risk of progression when using sonidegib compared to vismodegib was 59.1% (OR=0.409; 95% CI 0.229–0.732, p=0.0026, Z=3.013). The results of testing the hypothesis about the equality of the proportion of patients with laBCC without disease progression 12 months after the start of therapy also confirmed the presence of statistically significant differences in efficacy between the two treatments in favor of sonidegib (χ^2=9.2007, df=1, p=0.002419, 95% CI 0.09312–0.432132). The use of sonidegib in the 1-line of therapy, 2.53 million rubles per year will be required per 1 patient, which is 10.86% lower than the use of vismodegib, and corresponds to an absolute saving of 308.55 thousand rubles. The "cost-effectiveness" indicator (CER) for sonidegib was 114,627 rubles versus 220,295 rubles for vismodegib. The incremental cost-effectiveness ratio (ICER) is 175,050 rubles per additional month of PFS. Sensitivity analysis showed the stability of the results when changing key parameters.

Conclusion. Based on the results of the study, the hypothesis about the clinical and economic benefits of sonidegib in the treatment of laBCC was confirmed, and data were obtained on the clinical and economic feasibility of using sonidegib in widespread clinical practice.

Keywords: sonidegib; clinical and economic analysis; basal cell carcinoma; health technology assessment

Abbreviations: INN — an international nonproprietary name; GCM — general characteristic of medicines; VEM — list of vital and essential medicines; BCC — basal cell carcinoma; RCTs — randomized clinical trials; MSP — the maximum selling price; OV — overall survival; PFS — progression-free survival; OR — odds ratio; RR — relative risk.

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Клинико-экономические преимущества применения лекарственного препарата сонидегиб в терапии 1 линии пациентов с местно распространённым базальноклеточным раком кожи

О.И. Ивахненко[1], В.В. Ряженов[1], М.Ю. Фролов[2], В.А. Рогов[2]

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет), Россия, 119048, г. Москва, ул. Трубецкая, д. 8, стр. 2
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 400066, г. Волгоград, пл. Павших Борцов, д. 1

E-mail: oii@hta-expert.ru

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Одним из ключевых факторов доступности современных методов лечения и выбора оптимальной терапии для пациентов являются клинико-экономические характеристики новых медицинских технологий.

Цель. Оценка клинико-экономической целесообразности применения препарата сонидегиб в условиях широкой клинической практики.

Материалы и методы. В качестве методологической основы применялись общенаучные методы исследования. Для проведения клинико-экономической оценки была разработана модель по типу «дерева решений». Клинико-экономическая оценка применения препарата сонидегиб проведена с позиции системы здравоохранения РФ: учитывались затраты на системную лекарственную терапию 1 линии пациентов с местно распространённым базальноклеточным раком кожи (мрБКРК).

Результаты. Сравнительный анализ эффективности по критерию «выживаемость без прогрессирования» (ВБП) выявил преимущество сонидегиба над висмодегибом: отношение шансов (ОШ) прогрессии заболевания у пациентов с мрБКРК через 12 мес. с момента начала терапии составило 0,27778 (95% ДИ 0,125–0,618, p=0,0017, Z=3,1423). Снижение риска прогрессирования при использовании сонидегиба по сравнению с висмодегибом составило 59,1% (ОР=0,409; 95% ДИ 0,229–0,732, p=0,0026, Z=3,013). Результаты проверки гипотезы о равенстве долей пациентов с мрБКРК без прогрессии заболевания через 12 мес. после начала терапии также подтвердили наличие статистически значимых различий в эффективности между двумя методами лечения в пользу сонидегиба (χ^2=9,2007, df=1, p=0,002419, 95% ДИ 0,09312–0,432132). При использовании сонидегиба в 1 линии терапии потребуется 2,53 млн руб. в год в расчёте на 1 пациента, что на 10,86% ниже, чем при использовании висмодегиба, и соответствует абсолютной экономии в размере 308,55 тыс. руб. Показатель «затраты–эффективность» (CER) для сонидегиба составил 114 627 руб. против 220 295 руб. для висмодегиба. Инкрементальный показатель «затраты–эффективность» (ICER) равен 175 050 руб. за дополнительный месяц ВБП. Анализ чувствительности показал устойчивость результатов при изменении ключевых параметров.

Заключение. На основании результатов исследования была подтверждена гипотеза о клинико-экономических преимуществах сонидегиба при лечении мрБКРК и получены данные о целесообразности применения сонидегиба в условиях широкой клинической практики.

Ключевые слова: сонидегиб; клинико-экономический анализ; базальноклеточный рак кожи; оценка медицинских технологий

Список сокращений: ЛП — лекарственный препарат; МНН — международное непатентованное наименование; ОХЛП — общая характеристика лекарственного препарата; ЖНВЛП — перечень жизненно необходимых и важнейших лекарственных препаратов; БКРК — базально клеточный рак кожи; РКИ — рандомизированные клинические исследования; ПОЦ — предельная отпускная цена; ОВ — общая выживаемость; ВБП — выживаемость без прогрессирования; ОШ — отношение шансов; ОР — относительный риск.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common type of skin cancer, originating from basal cells, which are located in the lower layer of the epidermis. BCC accounts for about 80% of all skin cancer cases. According to statistics, most countries, especially those with high insolation, are experiencing an increase in the incidence of BCC [1, 2]. According to the American Cancer Society (2023), more than 5 million cases of BCC are diagnosed annually in the United States [3].

In Europe, the incidence rate varies from 20 to 200 cases per 100,000 population in different regions [2]. In Australia, keratinocyte carcinomas, including basal cell and squamous cell carcinomas, create a significant medical and financial burden for the population and the country's healthcare system [4]. According to the WHO, in 2022, skin cancer ranked 5th in terms of primary morbidity and 22nd in the structure of mortality due to oncopathology worldwide. In the Russian Federation, skin cancer (excluding melanoma) is among the oncopathologies that form 80% of the contingent of patients with malignant neoplasms (MNs). The absolute number of patients with skin MNs (ICD-10 C44) registered at the end of 2023 was 448,230 people. Since 2013, the prevalence of skin MN (excluding melanoma) has increased from 258.3 to 305.5 per 100,000 population. The proportion of patients with skin MNs (excluding melanoma) who were registered for 5 years or more in 2023 was 39.2%. In the overall structure of the contingent of patients with MNs registered for 5 years or more, its share was 7.2%. Skin MN (ICD-10 C44) are among the leading localizations and in the overall structure of MN morbidity — 13.6% in the general population, 11.2% among men and 15.6% among women. Over 10 years, the increase in age-standardized morbidity rates increased by 1.11% — from 25.14 in 2013 to 29.82 in 2023 per 100,000 population. In absolute terms, 91,867 people were registered with a diagnosis of skin MN (excluding melanoma) in 2023. The average age of patients with skin MN (excluding melanoma) is 70.2 years. At the same time, according to statistics, skin MN (excluding melanoma) are among the nosologies with the highest proportion in the age group from 30 to 59 years (8.3%), which determines the social significance of the disease among the economically active population of the Russian Federation. The proportion of skin MNs (excluding melanoma) detected at advanced stages in 2023 was 16.2%. BCC usually progresses slowly and rarely metastasizes, with mortality rates of less than 0.1% [3, 5]. Nevertheless, BCC causes serious complications, which, if not treated in a timely manner, can lead to significant changes in the skin and, as a result, to disability. Due to the heavy severity of the disease, BCC has high medical, social and economic significance and is characterised by a high burden on the healthcare system [6, 7].

The main methods of treatment for BCC are a surgical treatment and radiation therapy. In case of aggressive BCC with inoperable locally advanced or metastatic process or in case of ineffectiveness of previous methods of treatment, systemic drug therapy with Hedgehog signaling pathway inhibitors is recommended [7]. Currently, in the Russian Federation, there is only one non-alternative option for targeted therapy for such patients — vismodegib, which effectively blocks the Sonic Hedgehog (SHh) signaling pathway. In 2024, another Hedgehog inhibitor was registered in the Russian Federation — sonidegib.

One of the key factors in ensuring the availability of modern methods of treatment and choice an optimal therapy for patients is the clinical and economic characteristics of new medical technologies. In the Russian Federation, a pharmacoeconomic assessment of the sonidegib has not been previously conducted.

THE AIM of this study was to assess the clinical and economic feasibility of sonidegib in a wide clinical practice. To achieve this aim, the following objectives were solved:

- The characteristics of the new medical technology were determined: indications for use, administration regimen and dosage regimen, conditions of use in clinical practice;
- Modern approaches to the treatment of patients with BCC were studied to select alternative options for targeted therapy for conducting a clinical and economic assessment;
- A systematic search and review of papers on the comparative efficacy and (or) safety of sonidegib with selected alternatives was carried out to justify the choice of research method;
- Methods for accounting for direct medical costs and assessing clinical and economic indicators were developed;
- A mathematical model was developed for conducting a clinical and economic assessment of the use of sonidegib in the healthcare system of the Russian Federation.

MATERIALS AND METHODS

This study is based on the hypothesis of the clinical and economic feasibility of using the Hedgehog signaling pathway inhibitor — sonidegib — as part of the 1-line systemic therapy in patients with locally advanced BCC (laBCC). Developing the study design, general scientific methods were used to ensure a comprehensive and systematic approach to solving the objectives. To substantiate the hypothesis and develop the methodology for clinical and economic analysis, clinical guidelines for the diagnosis and treatment of patients with BCC, information from the State Register of Medicines, data on the comparative clinical efficacy

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and safety of sonidegib with selected alternatives, and information from the State Register of Maximum Selling Prices were used. The regulatory framework of the study was formed on the basis of the current legislation of the Russian Federation in the field of regulation of medical care and drug provision, technical regulation norms for conducting assessments of medical technologies, clinical and economic studies and budget impact analysis, enshrined in the documents of the national standardisation system.

The clinical and economic assessment of the use of the sonidegib was carried out from the position of the healthcare system of the Russian Federation: the study took into account only direct medical costs for the 1-line systemic drug therapy of patients with BCC. To conduct a clinical and economic assessment it was developed "decision tree" model. The concept of the model was to assess the clinical and economic effectiveness of the 1-line systemic therapy of BCC depending on the chosen treatment (Fig. 1).

The determination of potential alternatives was carried out on the basis of an analysis of the current national clinical guidelines (CG) for the diagnosis and treatment of BCC, approved by the Scientific and Practical Council of the Ministry of Health of Russia, approved by the developers of the CG and posted in the clinical guidelines rubricator. The choice of research method and efficacy criteria for conducting a clinical and economic assessment was carried out based on the results of a systematic search and review of papers on the efficacy of sonidegib in comparison with alternative. The time horizon of the study was 1 year. The calculation of the costs of drug therapy was carried out on the basis of information on the method of administration and dosage regimen of the drug, indicated in the general characteristics of the medicines (GCM). When calculating the costs of therapy, the duration of 1 month was taken as 30.44 days in accordance with Federal Law of RF No. 107-FZ dated June 03, 2011 (as amended on April 14, 2023) "On the Calculation of Time". The basis for the development of the study design, the structure of the model and the determination of key parameters for calculations is the algorithm presented in Figure 2.

Methodology for determining the characteristics of medical technology

Registered indications for medical use for the proposed medicine, its administration regimen (method of administration, recommended dosage) are determined on the basis of an analysis of information from the GCM sonidegib[1] (Table 1).

Based on the results of the analysis, the following theses were determined, which formed the basis for the development of the clinical and economic study design:

Sonidegib is a Hedgehog signaling pathway inhibitor, indicated for use in adults for the treatment of laBCC that is not amenable to surgical treatment or radiation therapy;

The medicine is intended for oral administration, the recommended dose is 200 mg 1 time per day;

Duration of use of the drug — in clinical studies, treatment with sonidegib continued until disease progression or until unacceptable toxicity developed.

Methodology for studying existing approaches to the treatment of patients with basal cell skin cancer. Determination of alternatives for comparison

The provision of medical care, including drugs, in the Russian Federation is regulated by the provisions of Federal Law No. 323: medical care is carried out "in accordance with the procedure for the provision of medical care, on the basis of clinical guidelines and on the basis of standards of medical care approved by the authorized executive authority" (Article 37, Chapter 5, Federal Law No. 323)[2].

The choice of medicines for the formation of treatment regimens was carried out according to the following algorithm:

- first, modern approaches to the diagnosis and treatment of BCC were studied and then were selected alternatives for comparison;
- then, information from the State Register of Medicines of RF and the current list of vital and essential medicines (VEMs) was analysed;
- further, information from the GCM on the corresponding drugs selected as alternatives for comparison was studied.

According to the provisions of the CG, the choice of treatment tactics for patients with BCC is carried out individually, taking into account the prevalence of the tumor process, its localisation, prognostic factors (clinical form, localisation of BCC, the rate of the tumor process, etc.), the general condition of the patient, the presence of concomitant pathologies, and the expected

[1] The register of OHLP and LV in the EAEU. Sonidegib. Available from: https://lk.regmed.ru/Register/EAEU_SmPC

[2] Federal Law No. 323-FZ dated November 21, 2011 (as amended on December 28, 2024) On the Fundamentals of Public Health Protection in the Russian Federation" (as amended and supplemented, introduction in effective from March 01, 2025). Russian

life expectancy. The main goal of treatment for patients with BCC is the complete removal of the tumor (elimination of the tumor process) with maximum preservation of the functioning of the involved organ and the best cosmetic results[3].

Patients with laBCC who are not amenable to surgical treatment and radiation therapy, in the absence of contraindications (severe concomitant pathology and immunodeficiency states), are recommended to undergo systemic therapy with vismodegib until disease progression or intolerance to treatment[4]. Currently, this is the only treatment option in the 1-line therapy of patients with BCC. A summary characteristic of the information justifying the choice of the comparison medicine is presented in Table 2.

Vismodegib is used for the same indications and in the same clinical situation as sonidegib, is registered in the Russian Federation, is included in the current CG[5] and in the list of VEM[6], which allows it to be used as a comparison medicine for conducting a clinical and economic assessment of the use of sonidegib in a wide clinical practice.

Methodology for conducting a systematic search and review for the selection of a study method and the determination of key parameters for calculations

A systematic search for information on the comparative clinical efficacy of sonidegib and vismodegib was carried out in accordance with the Cochrane and the European Network for Health Technology Assessment (EUnetHTA). The following databases were used as sources of information when conducting a systematic search: PubMed/MEDLINE, National Institutes of Health, Cochrane Library.

Searching in the PubMed/MEDLINE database, the following keywords and logical operators were used: “advanced basal cell carcinoma” AND “therapy”. In the international register NIH, an advanced search was carried out using the following filters: condition OR disease — advanced basal cell carcinoma; status — completed; phase — phase 2 or 3; age group — adult. For the Cochrane Library, the following search strategy was used: MeSH descriptor: [advanced basal cell carcinoma] explode all trees and with qualifier(s): [therapy — TH]. When searching, restrictions on the language of scientific publications (English) were taken into account as filters. The time horizon of the search was not limited. The initial search for research results was carried out during the development of the study design and the development of the model (August 2024), an additional search was carried out at the validation stage in order to check for new data (October 2024).

The following criteria were taken into account when selecting studies: study design (comparative randomized clinical trials (RCTs), RCTs with a non-comparative design, non-randomized studies, indirect comparisons), description of the demographic characteristics of patients, allowing for an assessment of the comparability of groups between studies, the presence of Kaplan–Meier survival curves with data on progression-free survival (PFS). If there are results with PFS indicators for a longer observation period, current information on the efficacy for medical technologies included in the study was taken into account.

Based on the results of a systematic search and review, no direct comparative studies of the efficacy and safety of sonidegib and vismodegib were found. After studying the abstracts and removing duplicates of published research results, the following works were selected for further analysis: naive indirect adjusted comparison by Odom et al. (2017) [8] and published results of studies BOLT [9–11] and ERIVANCE [12–14].

In the study by Odom et al. (2017), the “matching-adjusted indirect comparison” (MAIC) method was used to adjust for differences in the baseline characteristics of patients between studies, taking into account two key factors — the proportion of patients who received previous radiation therapy and surgical treatment. After weighting, the objective response rates and median PFS in patients receiving sonidegib practically did not change (ORR: 56.1% before and 56.7% after weighting; PFS: 22.1 months before and after weighting). For vismodegib, the corresponding figures were 47.6% and 9.5 months. The authors noted the absence of a significant impact of the correction of individual patient data from the BOLT study on the efficacy of the drug according to the PFS criterion — the median PFS before and after correction was 22.1 months (95% CI 14.8–NE — not estimable / not amenable to assessment) [11]. This suggests that differences in populations did not have a statistically significant impact on absolute or relative effect indicators [15].

[3] Clinical Guidelines. Basal cell carcinoma of the skin; 2024.
[4] Ibid.
[5] Ibid.
[6] Decree of the Government of the Russian Federation dated October 12, 2019 No. 2406-r (as amended on January 15, 2025) On approval of the list of vital and essential medicines, as well as lists of medicines for medical use and the minimum range of medicines required for medical care. Russian

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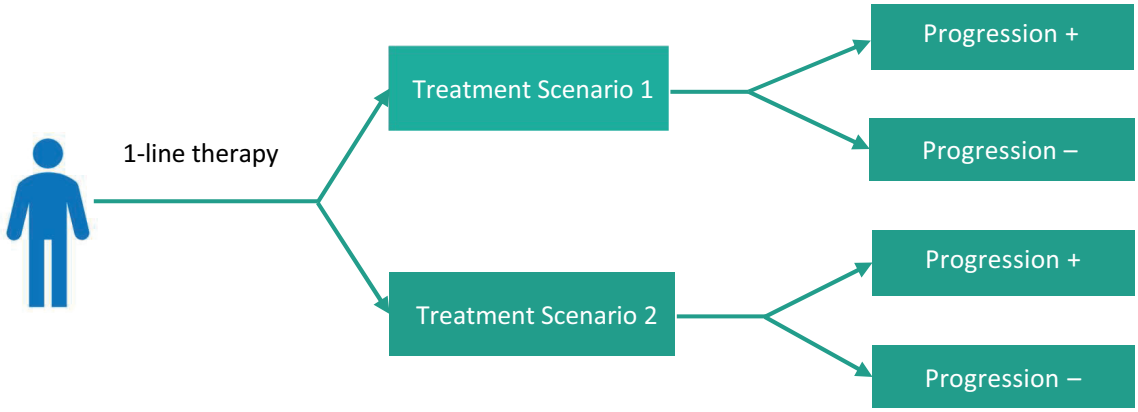

Figure 1 – Model diagram for conducting a clinical and economic assessment.

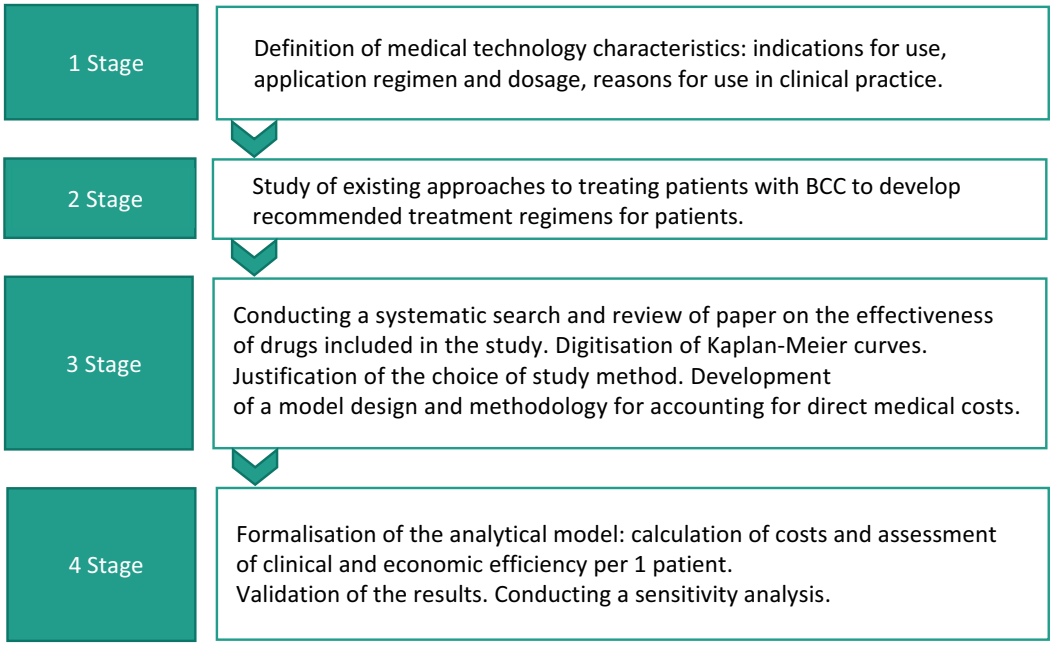

Figure 2 – Algorithm for developing the study design, the structure of the analytical model and determining key parameters for conducting a clinical and economic assessment.
Note: BCC — basal cell carcinoma.

Table 1 – Characteristics of the medical technology

INN / T	Characteristics	Medication elease form and dosage	Registration status of medicine in RF	Indications for use	Recommended dose and administration regimen
Sonidegib (Ozomdo)	ATC code: L01XJ02; PTG: antitumor agents, other antitumor agents; MA: Hedgehog signaling pathway inhibitors.	Capsules 200 mg, No. 30	LP-No. (006795)-(RG-RU) 05.09.2024	Sonidegib is indicated for use in adults for the treatment of locally advanced BCC that is not amenable to surgery or radiation therapy.	The recommended dose of sonidegib is 200 mg, orally, 1 time per day. Treatment should be continued until disease progression or unacceptable toxicity develops

Note: INN — international nonproprietary name; TN — trade name; PTG — pharmacotherapeutic group; ATC — Anatomical Therapeutic Chemical classification; MA — mechanism of action; BCC — basal cell carcinoma.

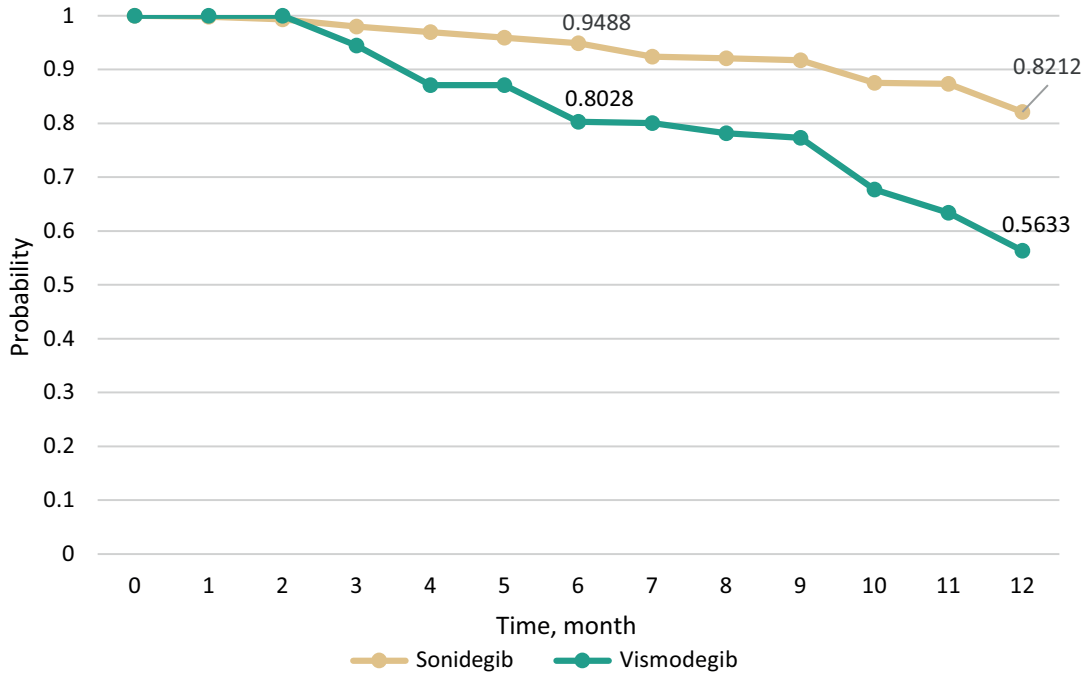

Figure 3 – Results of the restoration of individual patient data from studies (compiled by the authors according to the data from the BOLT [10] and ERIVANCE [12] studies).

Figure 4 – Change in cost–effectiveness (CER) values when varying the efficacy and prices of sonidegib and vismodegib within the sensitivity analysis compared to the results of basic calculations.
Note: PFS — progression-free survival; MSP — maximum selling prices.

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Table 2 – Characteristics of medicines used for the 1-line of therapy of patients with metastatic and unresectable basal cell carcinoma who are not amenable to surgical treatment and radiation therapy

INN	Indications for use	Registration status in the Russian Federation	Availability of recommendations for use for the target indication in clinical guidelines	Availability in the lists of drugs for medical use
Vismodegib	Vismodegib is indicated for use in adults over 18 years of age for treatment of metastatic or locally advanced BCC: in case of recurrence after surgical treatment; if surgical treatment or radiation therapy is not advisable.	LP-No. (001355)-(RG-RU), 27.10.2022; original drug (TN: Erivedge®); LP-No. (004472)-(RG-RU), 01.02.2024, reproduced drug (TN: Vismodegib-Promomed).	Included in the CG, 1-line of therapy.	The drug vismodegib is included in the list of VEM: L01XX other antitumor medicine; capsule dosage form.

Note: INN — international nonproprietary name; TN — trade name; CG — clinical guidelines; VEM — list of vital and essential medicines.

Table 3 – Four-field contingency table for calculating the odds ratio of progression in patients with locally advanced basal cell carcinoma when using alternative therapeutic options

Alternative therapeutic options	Outcomes 12 months after the start of therapy		Total
	Progression+	Progression–	
Sonidegib	12	54	66
Vismodegib	28	35	63
Total	39	90	129

Table 4 – Results of calculating relative risk and odds ratio with confidence intervals, Z-statistics and p-values

Indicator	Assessment	95% CI lower limit	95% CI upper limit	*Z*	*p*
OR	0.278	0.125	0.618	–3.143	0.0017
RR	0.409	0.229	0.732	–3.013	0.0026

Note: OR — odds ratio; RR — relative risk; CI — confidence interval.

Table 5 – Results of testing the hypothesis on the equality of the proportions of patients with locally advanced basal cell carcinoma without disease progression 12 months after the start of therapy with compared medicines

Alternative therapeutic options	Number of patients with laBCC without disease progression 12 months after the start of therapy	Total patients in the sample [10, 12]	Proportion of patients with laBCC without disease progression 12 months after the start of therapy	Test results
Sonidegib	54	66	0,8212	χ^2=9.2007 df=1 *p*=0.002419 95% CI 0.09312–0.432132
Vismodegib	35	63	0.5633	

Note: laBCC — locally advanced basal cell carcinoma.

Table 6 – Price of drugs used when accounting for the costs of the 1st line drug therapy (base scenario)

INN	Release form	Administration regimen and dosage regimen	Maximum selling price of the manufacturer without VAT / with VAT, rubles, (USD)[7]	Price per 1 unit without VAT / with VAT, rubles.** (USD)[8]	Costs for 1 month of therapy with VAT, rubles.*** (USD)[9]
Vismodegib	Capsules 150 mg, No. 28	150 mg 1 time per day	198 051.61 / 217 856.77 (2 058.83 / 2 264.71)*	7 073.27 / 7 780.60 (73.53 / 80.88)*	236 817.11 (2461.81)*
Sonidegib	Capsules 200 mg, No. 30	200 mg 1 time per day	189 158.29 / 208 074.12 (1 966.38 / 2 163.02)*	6 305.28 / 6 935.80 (65.55 / 72.10)*	211 104.20 (2 194.52)*

Note: * The average value of the dollar exchange rate in relation to the ruble was used in the calculations: 96.1962 rubles per 1 USD for October 2024; **Costs per 1 administration, rubles;*** In the calculations, the duration of 1 month was taken as 30.44 days in accordance with Federal Law "On the Calculation of Time" dated June 3, 2011 N 107-FZ. INN — international nonproprietary name.

Table 7 – Price of medicines used when accounting the costs of the 1-line drug therapy when conducting a sensitivity analysis

INN	Base value of the maximum selling price without VAT / with VAT, rubles. (USD)*	Change in the maximum selling price of the manufacturer	Key parameters for calculating direct medical costs when conducting a sensitivity analysis*		
			Value of the MSP without VAT / with VAT rubles. (USD) within the SA	Price per 1 unit without VAT / with VAT, rubles (USD)	Costs for 1 month of therapy, rubles. (USD) with VAT**
Key parameters for calculating direct medical costs when changing the MSP for sonidegib and the base value of the MSP for vismodegig					
Visodegib	198 051.61 / 217 856.77 (2 058.83 / 2 264.71)	No changes	198 051.61 / 217 856.77 (2 058.83 / 2 264.71)	7 073.27 / 7 780.60 (73.53 / 80.88)	236 817.11 (2 461.81)
Sonidegib	189 158.29 / 208 074.12 (1 966.38 / 2 163.02)	Increase in the range from 5 to 20% with a step of 5% (+5%)	198 616.20 / 218 477.82 (2 064.70 / 2 271.17)	6 620.54 / 7 282.59 (68.82/ 79.22)	221 659.41 (2 304.24)
		+10%	208 074.12 / 228 881.53 (2 163.02 / 2 379.32)	6 935.80 / 7 629.38 (89.61/ 100.01)	232 214.62 (2 413.97)
		+15%	217 532.03 / 239 285.23 (2 261.34 / 2 487.47)	7 251.07 / 7 976.17 (110.41 / 120.80)	242 769.82 (2 523.70)
		+20%	226 989.95 / 249 688.94 (2 359.66 / 2 595.62)	7 566.33 / 8 322.96 (131.20 / 141.59)	253 325.03 (2 633.42)
Key parameters for calculating direct medical costs when changing the MSP for vismodegib and the base value of the MSP for sonidegib					
Vismodegib	198 051.61 / 217 856.77 (2 058.83 / 2 264.71)	Reduction of the base value of the MSP by 22.5% to the MSP for the generic vismodegib	161 605.16 (1 679.95)	5 771.61 / 6 348.77 (60.00 / 66.00)	193 129.71 (2 008.78)
Sonidegib	189 158.29 / 208 074.12 (1 966.38 / 2 163.02)	No changes	189 158.29 / 208 074.12 (1 966.38 / 2 163.019)	6 305.28 / 6 935.80 (65.55 / 72.10)	211 104.20 (2 194.52)
Key parameters for calculating direct medical costs when changing the MSP for sonidegib and vismodegib					
Vismodegib	198 051.61 / 217 856.77 (2 058.83 / 2 264.71)	Reduction of the base value of the MSP by 22.5% to the MSP for the generic vismodegib	161 605.16 (1 679.95)	5 771.61 / 6 348.77 (60.00 / 66.00)	193 236.84 (2 008.78)
Sonidegib	189 158.29 / 208 074.12 (1 966.38 / 2 163.02)	Reduction of the base value of the MSP by 10%	172 361.03 (1 791.77)	5 745.37 / 6 319.90 (59.73 / 65.70)	192 358.14 (1 999.64)

Note: * The calculations used the average exchange rate of the dollar against the ruble: 96.1962 rubles per 1 USD for October 2024. ** In the calculations, the duration of 1 month was taken as 30.44 days in accordance with Federal Law No. 107-FZ of June 3, 2011 "On the Calculation of Time". INN — international non-proprietary name; MSP — maximum selling price.

[7] The dynamics of the official exchange rate of a given currency: the US dollar from October 1, 2024 to October 31, 2024. The Bank of Russia. Available from: https://cbr.ru/currency_base/dynamics/

[8] Ibid.

[9] Ibid.

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Table 8 – Costs of 1-line therapy per 1 patient with locally advanced basal cell carcinoma per year, rubles

INN	Application scheme	Price per 1 unit without VAT, rubles (USD)	Price per 1 unit with VAT, rubles (USD)	Costs per month, rubles (USD)	Therapy costs per year, rubles (USD)
Vismodegib	150 mg 1 time per day	7 073.27 (73.53)*	7 780.60 (80.88)*	236 817.11 (2 461.81)*	2 841 805,35 (29 541,76)*
Sonidegib	200 mg 1 time per day	6 305.28 (65.55)*	6 935.80 (72.10)	211 104.20 (2 194.52)*	2 533 250,35 (26 334,21)*
Difference in costs between medicines		768,00 (7,98)*	844.79 (8.78)*	25 712.92 (267.30)*	308 555.00 (3207.56)*
Percentage of cost deviation, %					10.86%

Note: * The calculations used the average exchange rate of the dollar against the ruble: 96.1962 rubles per 1 USD for October 2024. INN — international non-proprietary name.

Table 9 – Results of sensitivity analysis to changes in medicine prices

Alternative therapeutic options	Basic MSP value without VAT used in calculations, rubles (USD)*	Change in MSP without VAT within the sensitivity analysis, rubles (USD)*	Difference in costs, rubles (USD)*	Percentage of cost deviation, % / differences in costs for sonedigib compared to costs for vismodegib[10]
Scenario 1 of changes in drug prices: increase in MPC for sonidegib with the basic value of MPC for vismodegib				
Vismodegib	198 051.61 (2 058.83)	198 051.61 (2 058.83)	–	–
Sonidegib	189 158.29 (1 966.38)	198 616.20 (+5%) (2 064.70)	-181 892.48 (-1 890.85)	-6.40 % insignificant differences
		208 074.12 (+10 %) (2 163.02)	-55 229.96 (-574.14)	-1.94 % insignificant differences
		217 532.03 (+15%) (2 261.34)	+71 432.55 (742.57)	+2.51% insignificant differences
		226 989.95 (+20 %) (2 359.66)	+197 985.24 (2 058.14)	+6.97 % insignificant differences
Scenario 2 of changes in drug prices: decrease in MPC for vismodegib with the basic value of MPC for sonidegib				
Vismodegib	198 051.61 (2 058.83)	161 605.16 (1 679.95)	+214 289,33 (2 227,63)	9.25% insignificant differences
Sonidegib	189 158.29 (1 966.38)	189 158.29 (1 966.38)		
Scenario 3 of changes in drug prices: decrease in MPC for both medicines				
Vismodegib	198 051.61 (2 058.83)	161 605.16 (1 679.95)	-10 538.60 (109.55)	0.45% parity costs
Sonidegib	189 158.29 (1 966.38)	172 361.03 (1 791.77)		

Note: * The calculations used the average exchange rate of the dollar against the ruble: 96.1962 rubles per 1 USD for October 2024. INN — international non-proprietary name; MSP — maximum selling prices.

[10] Decree of the Government of the Russian Federation dated August 28, 2014 No. 871 (as amended on July 25,2024) On Approval of the Rules for the Formation of Lists of medicines for medical use and the minimum range of medicines required for medical care. Russian

To assess the comparative efficacy according to the criterion "disease progression in patients with laBCC receiving therapy with sonidegib and vismodegib", the relative risk (RR) and odds ratio (OR) were calculated. The calculations were performed on the basis of digitised Kaplan–Meier curves from the BOLT [10] and ERIVANCE [12] studies. The digitization of Kaplan-Meier curves was carried out according to the method of Guyot et al. [16] using the Engauge Digitizer[11] utility, which allowed to restore individual patient data for subsequent analysis. The results of the restoration of individual patient data are presented in Figure 3.

The initial data for calculating RR and OR are presented in the form of a four-field contingency table, reflecting the number of events and the total number of patients in each group (Table 3).

To calculate OR, confidence interval (95% CI), *p-value* and *Z-score* and relative risk (RR), the R version 4.4.3 environment was used. The calculations were carried out according to generally accepted statistical formulas, standardly used in epidemiology and medical statistics[12].

OR 12 months after the start of therapy was 0.27778 (95% CI 0.125–0.618, p = 0.0017, Z = 3.143). The chances of progression on vismodegib therapy in patients were statistically significantly higher (OR < 1, 95% CI did not cross 1) compared to the use of sonidegib, which allows us to conclude that sonidegib is more effective according to the PFS criterion. The probability of progression in the sonidegib and vismodegib groups was 0.182 (18.2%) and 0.444 (44.4%), respectively, and the RR was 0.409 (95% CI 0.229–0.732, p = 0.0026; Z = 3.013). Thus, the reduction in the risk of progression when using sonidegib compared to vismodegib is 59.1%.

To confirm the presence of statistically significant differences in efficacy between sonidegib and vismodegib, a hypothesis test was also conducted on the equality of the proportions of patients with laBCC who did not have disease progression 12 months after the start of therapy. At the first stage, the null hypothesis (H0) was formulated: the proportions of patients without disease progression in the groups receiving sonidegib and vismodegib do not differ statistically significantly and any observed differences are due to random factors. The alternative hypothesis (H1) assumed the presence of a statistically significant difference in the efficacy of the two treatment methods, expressed in the difference in the proportions of patients without progression 12 months after the start of therapy. A significance level of $\alpha = 0.05$ was used to test the hypothesis.

Data analysis and assessment of the statistical significance of differences between proportions were carried out in the statistical environment R version 4.4.3 using the prop.test() function. This function implements a *z*-test for comparing proportions using statistics based on an approximation to the χ^2 distribution, taking as arguments the number of successful outcomes (number of patients without progression) and the total number of observations in each group. The prop.test() function also allows you to calculate the *p-value*, CI for the difference in proportions and the value of the test statistic, which provides a comprehensive assessment of the presence of statistically significant differences between groups. The results of the *z*-test for the equality of proportions are presented in Table 5.

The test results demonstrated statistically significant differences, which is consistent with the calculations of OR and RR and further confirms the advantage of sonidegib in efficacy according to the PFS criterion. Thus, the conclusions obtained justify the choice of the "cost–effectiveness" method for further clinical and economic assessment of the use of sonidegib.

Methodology for developing a model for conducting a clinical and economic assessment of the use of the sonidegib in a wide clinical practice

To analyze the economic consequences of the use of sonidegib in a wide clinical practice, a model was developed according to the "decision tree". A graphical diagram of the model is presented earlier in Figure 2. Based on the results of determining the characteristics of the new medical technology, studying existing approaches to the treatment of patients with BCC and selecting alternatives for comparison, a systematic search and review of data on the comparative efficacy of alternative technologies for selecting a research method, the model included 2 alternative scenarios for the treatment of patients with laBCC in the 1-line of therapy:

- Scenario 1 — the use of vismodegib in the 1-line of therapy of patients in the target population;
- Scenario 2 — the use of sonidegib in the 1-line of therapy of patients in the target population.

[11] Engauge Digitizer. Available from: http://digitizer.sourceforge.net/
[12] Medical and biological statistics [text]. Stanton gloss; Buzikashvili NE, Samoilova DV, editors; Moscow: Pravda; 1999. 459 p. Russian

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The current national CG do not provide recommendations for the treatment of patients with laBCC after disease progression during therapy with SHh signaling pathway inhibitors. In this regard, when conducting a clinical and economic assessment, a conservative scenario was considered, i.e. only direct costs for the 1-line therapy were taken into account. However, it should be noted that in the practical recommendations of the Russian Society of Clinical Oncology, in case of ineffectiveness or intolerance of the 1st line targeted therapy, immune checkpoint inhibitors, or PD-1 inhibitors — cemiplimab, nivolumab, pembrolizumab are used as drugs of choice in the 2-line [7]. The lack of accounting for costs and efficacy in the 2-line may lead to an incomplete assessment of the clinical and economic efficacy of sonidegib, which is a limitation of this study.

Methodology for accounting for costs when conducting a clinical and economic assessment

The calculation of the costs of drug therapy for the interventions under consideration was carried out on the basis of information on the methods of administration and dosage regimens indicated in the GCM. Information on prices for vismodegib was used as a source of information on the current registered maximum selling price (MSP) of the manufacturer, posted in the State Register of Registered Prices for Medicines[13]. During 2024, the generic of the original vismodegib was not purchased at the expense of budgetary funds to ensure state and municipal needs. Nevertheless, to assess the potential impact of participation in the procurement of the original and reproduced medicine, the average registered MSP within the INN vismodegib was taken into account. Data on the MSP planned for registration for the medicine proposed for inclusion were provided by the manufacturing company. The duration of 1 month was taken as 30.44 days. The calculations took into account the allowances established by the legislation of the Russian Federation (VAT 10%). Key parameters for calculating the costs of conducting the 1st line therapy in the base scenario are given in Table 6.

Methodology for calculating clinical and economic indicators

The calculation of cost–effectiveness ratio (CER) indicators was carried out to the generally accepted methodology. Data on the clinical efficacy of alternative technologies and information on the costs of drug therapy depending on the chosen treatment scenario were used to calculate CER[14]:

$$CER_i = \frac{Cost_i}{Ef_i},$$

where CER_i — cost–effectiveness ratio when using therapy scenario i; $Cost_i$ — costs per 1 patient per course of therapy using scenario i; Ef_i — efficacy of therapy using scenario i.

The incremental cost–effectiveness ratio (ICER) was also calculated to assess the clinical and economic benefits of sonidegib in the population of patients continuing the 1-line therapy by the end of 1 year of treatment. To calculate ICER, data on the clinical efficacy of alternative technologies from the BOLT [10] and ERIVANCE [12] studies, and the costs of drug therapy in the case of using each of the options included in the study were used[15]:

$$ICER = \frac{\Delta Cost}{\Delta Ef},$$

where ICER — incremental cost–effectiveness ratio; ΔCost — the difference in the costs of therapy between alternative treatment scenarios in the 1-line of therapy; ΔEf — the difference in efficacy between alternative treatment scenarios in the 1-line of therapy.

Analysis of the sensitivity of the results to changes in input parameters

To study the stability of the results obtained to changes in the key parameters used in the calculations, a sensitivity analysis was carried out to changes in the MSP for medicine and efficacy indicators.

To assess the stability of the results obtained to changes in the efficacy of sonidegib, a one-factor analysis of the sensitivity was carried out to changes in the base value of the median PFS (22.1 months) within the confidence interval. To assess the stability of the results obtained to changes in the efficacy of vismodegib, a one-factor analysis of the sensitivity was carried out to changes in the base value of the median PFS within the CI.

To assess the stability of the results obtained to changes in the MSP for sonidegib and vismodegib, 3 variants of sensitivity analysis were carried out:

In the first variant analysis for sonidegib, the base

[13] The State register of marginal selling prices. Vismodegib. Available from: https:// grls.minzdrav.gov.ru/PriceLims.aspx

[14] Clinical and economic analysis; Vorobyev PA, Avksentieva MV, Yuryev AS, et al. Moscow: Newdiamed; 2004. 404 p. Russian

[15] Ibid.

value of the MSP was 189 158.29 rubles per package, varied in the range from +5 to +20% with a step of 5%. The initial value of the MSP for vismodegib did not change.

In the second variant base value of the MSP of sonidegib, the initial value of the MSP of vismodegib was reduced by 22.5% to the MSP for the reproduced drug.

The third variant assessed the stability of the results obtained when the MSP for vismodegib was reduced by 22.5% and the MSP for vismodegib was reduced by 10%.

Key parameters for conducting the analysis of the sensitivity according to the price criterion for drugs are given in Table 7.

Research period

The economic consequences of the proposed inclusion of the sonidegib were assessed within 1 year.

Discounting

As the modeling period was 1 year, discounting was not used to bring future cash income to the present moment.

RESULTS

Hedgehog (Hh) inhibitors are a key group of targeted medicines aimed to block the Hedgehog signaling pathway, which plays an important role in the pathogenesis of BCC [17, 18]. Hedgehog inhibitors are the only option for treating patients with progressive BCC when surgery or radiation therapy is not possible [19, 20].

The most studied and clinically significant representatives of this group are vismodegib and sonidegib. Vismodegib became the first Hedgehog signaling pathway inhibitor to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic and locally advanced BCC that has recurred after surgery or when surgery or radiation therapy is not possible [21]. The efficacy and safety of vismodegib was studied in the international multicenter phase II ERIVANCE study, which included 104 patients with metastatic and locally advanced BCC. The primary endpoint of the study was to assess the objective response to therapy (reduction in tumor size). Secondary outcomes included objective response rate, duration of response to therapy, PFS, and overall survival (OS). According to the results of the study, in patients with locally advanced BCC and metastatic BCC who received vismodegib, the overall response rate (ORR) was 43% according to the assessment of an independent expert commission and 60% according to the assessment of local researchers for the cohort of laBCC, and for the cohort of metastatic BCC — 30 and 45%, respectively. The median duration of response was 7.6 months, and PFS was 9.5 months in both cohorts. After 39 months of follow-up, the ORR according to local investigators was 60.3% for the group of patients with laBCC and 48.5% for patients with metastatic BCC. The median duration of response was 26.2 months for laBCC and 14.8 months for metastatic BCC. The median OS could not be established in the cohort of laBCC, while in the cohort of metastatic BCC it was 33.4 months [12–14]. In 2015, the FDA and EMA approved another Hedgehog inhibitor, sonidegib (TN Odomzo®)[16], for the treatment of adult patients with laBCC, with recurrence after surgery or radiation therapy, or patients who are not candidates for surgery or radiation therapy. The efficacy and safety of the medicine was studied in an international multicenter double-blind randomized non-comparative phase II BOLT study involving 230 patients. The primary endpoint of the study was ORR, the proportion of patients with the best overall response. Secondary endpoints included response rate and duration, progression-free survival PFS OS, and safety. The ORR in patients with laBCC was 56% (95% CI 43–68). The median PFS was 22.1 months (95% CI not reached), the median duration of response to therapy was 26.1 months (95% CI not reached) when sonidegib was used at a dose of 200 mg once daily. Most adverse events were manageable and reversible with interruption of therapy or dose reduction. The median duration of sonidegib therapy was 11.0 months — 68% of patients took the drug for 8 months or more, 43% of patients — 12 months or more, 24% of patients — 20 months or more [9–11]. In the Russian Federation, the drug sonidegib became available in 2024.

To date, only one Hedgehog inhibitor, vismodegib, is included in the Formulary and the List of Vital and Essential Medicines. The medicine is recommended for use in the 1st line of therapy in adults over 18 years of age for the treatment of metastatic or locally advanced BCC with recurrence after surgical treatment or the impracticality of surgical treatment or radiation therapy.

[16] European Medicines Agency. Odomzo (Sonidegib). Available from: https://www.ema.europa.eu/en/ medicines/human/EPAR/odomzo#authorisation-details

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No direct comparative studies of the efficacy and safety of sonidegib and vismodegib have been conducted. Based on our own calculations, the OR of disease progression in patients with laBCC receiving therapy with sonidegib and vismodegib after 12 months from the start of therapy was 0.27778 (95% CI 0.125–0.618; p = 0.0017; Z = 3.143). The probability of progression in the sonidegib and vismodegib groups was 0.182 and 0.444, respectively, and the OR was 0.409 (95% CI 0.229–0.732). Thus, the reduction in the risk of progression when using sonidegib compared to vismodegib was 59.1%. The results of data analysis and assessment of the significance of differences between the proportions of patients without disease progression when using sonidegib and vismodegib also made it possible to draw conclusions about significant differences in clinical outcomes between the analyzed technologies according to the PFS criterion — χ^2 = 9.2007, df = 1, p = 0.002419, 95% CI 0.09312–0.432132.

Based on the method of assessing direct costs, the cost of 1-line therapy per 1 patient when using vismodegib will be 2.84 million rubles per year, in the case of using sonidegib — 2.53 million rubles per year. The difference in costs between alternative treatment scenarios in absolute terms is 308.55 thousand rubles (or 10.86%) per 1 patient in favor of sonidegib (Table 8).

According to the data obtained, the use of sonidegib with greater efficacy requires lower costs. With the basic values of the median PFS for sonidegib and vismodegib of 22.1 and 12.9 months, respectively, the CER indicator was 114 626.71 rubles for sonidegib and 220 294.99 rubles for vismodegib, which indicates the clinical and economic advantages of sonidegib. Changes in the efficacy of sonidegib and vismodegib (median PFS) within the CI showed the stability of the results obtained in the study: the use of sonidegib remains the dominant technology in terms of CER when varying the values of the efficacy indicator and medicine prices (Fig. 4).

With a difference in efficacy according to the PFS criterion between the sonidegib and vismodegib of 9.2 months, the ICER for sonidegib was 175 050.21 rubles per 1 unit of additional efficacy — 1 month of PFS. With a decrease in the efficacy of sonidegib to the lower limit of the CI (PFS 14.8 months) and the basic value of the median PFS for vismodegib of 12.9 months, the ICER for sonidegib will be 36 527.03 rubles per 1 month of PFS with a difference in efficacy of 1.9 months. With an initial PFS value for sonidegib of 22.1 months and an increase in the efficacy of vismodegib to the upper limit of the CI (median PFS 14.8 months), the ICER for sonidegib will be 158 973.90 rubles per 1 month of PFS with a difference in efficacy of 7.3 months.

With statistically significant advantages in the efficacy of sonidegib, the percentage of cost deviation in the basic scenario was “-10.86%” in favor of sonidegib. In absolute terms, the savings per 1 patient was 308.55 thousand rubles per patient.

To interpret the results obtained regarding the difference in costs, we used the provisions of the rules for forming lists of medicinal products for medical use[17]. If the clinical efficacy of a medicine is statistically significantly higher compared to an alternative treatment option, and the difference in direct medical costs is more than 10%, then the use of such a drug is characterized by lower costs. Thus, we can say that the use of sonidegib is characterized by lower costs for therapy compared to vismodegib with statistically significantly greater efficacy according to the PFS criterion.

As part of the sensitivity analysis, it was shown that the economic feasibility of using sonidegib in the 1st line is maintained in the range of increasing MPC for the medicine from 5 to 20% with participation in procurement to ensure state and municipal needs for both the original and reproduced medicine within the INN vismodegib. With an increase in the price of sonidegib from 5 to 20%, a gradual decrease in the economic benefit of sonidegib is observed, however, even with the maximum price increase (+20%), the difference in costs is +6.97% and is considered “insignificant”[18]. This indicates that the results are resistant to changes in the price of sonidegib in this range.

With a decrease in the price of vismodegib to 161 605.16 rubles (the price of the reproduced drug) and the basic value of the price of sonidegib (189 158.29 rubles), the percentage of cost deviation between alternative treatment scenarios will increase to +9.25%, which also does not lead to a significant increase in direct costs when providing medical care to patients with laBCC[19]. A decrease in prices for both medicines leads to a decrease in the difference in

[17] Decree of the Government of the Russian Federation dated August 28, 2014 No. 871 (as amended on July 25,2024) On Approval of the Rules for the Formation of Lists of medicines for medical use and the minimum range of medicines required for medical care. Russian
[18] Ibid.
[19] Clinical Guidelines. Basal cell carcinoma of the skin; 2024.

costs (to parity of 0.45%). The results of the sensitivity analysis are shown in Table 9.

A comparative analysis of efficacy according to the PFS criterion revealed the advantage of sonidegib over vismodegib: OR of disease progression in patients with laBCC 12 months after the start of therapy 0.27778 (95% CI 0.125–0.618, p = 0.0017; Z = 3.1423). The reduction in the risk of progression when using sonidegib compared to vismodegib is 59.1% (OR = 0.409; 95% CI 0.229–0.732, p = 0.0026; Z = 3.013). The hypothesis about the equality of the proportions of patients with laBCC without disease progression 12 months after the start of therapy also made it possible to draw conclusions about the presence of statistically significant differences in efficacy between the two treatment methods in favor of sonidegib — χ^2 = 9.2007, df = 1, p = 0.002419, 95% CI 0.09312–0.432132.

The cost of the therapy with sonidegib for 1 year per 1 patient was 2.53 million rubles, which is 10.86% lower compared to vismodegib, which corresponds to an absolute savings of 308.55 thousand rubles per 1 patient. Thus, with greater efficacy, the use of sonidegib requires lower costs.

The CER indicator for sonidegib is lower (114 626.71 rubles) compared to vismodegib (220 294.99 rubles), which also indicates the clinical and economic advantages of sonidegib. Changes in key parameters for calculation within the sensitivity analysis did not affect the results. According to the CER indicator, the use of sonidegib remains the dominant technology even with a median PFS value of 14.8 months — CER for sonidegib is 171 165.56 rubles, which is lower than CER for vismodegib both at the initial efficacy values for the medicine and with an increase in the efficacy of vismodegib within the CI (192 013.87 rubles). With a difference in efficacy according to the PFS criterion between sonidegib and vismodegib of 9.2 months, the ICER for sonidegib was 175 050.21 rubles per 1 unit of additional efficacy — 1 month of PFS.

DISCUSSION

A clinical and economic assessment of the use of the sonidegib was carried out from the perspective of the healthcare system in the short term in this study. It seems appropriate to further study the clinical and economic characteristics of sonidegib in the long term in terms of its impact on overall survival rates and the achievement of the targets of the national project “Combating Oncological Diseases” [23, 24].

A promising direction for further analysis of the clinical and economic consequences of the use of sonidegib in widespread practice is also the use of more complex mathematical models. The results obtained by Purser et al. are of interest, for example [25]. The authors developed a partitioned survival model to analyze expected direct medical costs, life-years gained (LYG), and quality-adjusted life-years (QALY) within the time period of survival of patients with laBCC. According to the modeling results, LYG without discounting when using sonidegib and vismodegib was 3.89 years for both comparators. At the same time, the expected direct medical costs for sonidegib were lower compared to vismodegib and amounted to £108 037 and £129 435, respectively. The expected discounted QALY indicators for sonidegib and vismodegib were 2.58 and 2.46, respectively. Sensitivity analysis showed that the results are resistant to uncertainty and variability of key parameters used for calculations. According to the authors, sonidegib is the dominant technology in terms of QALY and lower costs. Thus, models based on partitioned survival are an effective tool for assessing the clinical and economic benefits of sonidegib in the long term.

Since clinical and economic models are limited by the availability and quality of source data, it is also advisable to take into account data from real clinical practice, which will allow taking into account a wider range of clinical outcomes and increase the accuracy of the assessment [25].

From a practical point of view and adaptation in relation to the conditions of real clinical practice, the results obtained in the study by García et al. are also of interest [26]. The authors conducted a comparative assessment of the efficacy and safety of sonidegib and vismodegib based on available data from the BOLT and ERIVANCE studies using effect size indicators: the number of patients who need to be treated to achieve a favorable effect (Number Needed to Treat — NNT), the number of patients who must be exposed to risk over a certain period so that one of them develops an adverse outcome (Number Needed to Harm — NNH), and the benefit-risk ratio when taking the medicine (Likelihood to be helped or harmed — LHH). The authors calculated the NNT indicator for sonidegib and vismodegib based on data on ORR. The NNH indicator was calculated using data on treatment discontinuation

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due to adverse events and the frequency of adverse events. The LHH ratio was calculated as the ratio of the corresponding NNH to NNT values for each drug.

For sonidegib (dose 200 mg), the NNT indicator (the number of patients needed to treat to achieve one objective response, ORR) after 18 months was 1.65 (95% CI 1.35–2.01), while for vismodegib (150 mg) after 21 months — 2.10 (95% CI 1.65–2.82). The NNH indicator (the number of patients needed to observe one case of an adverse event leading to treatment discontinuation) was 1.9 (95% CI 1.6–2.5) for sonidegib and 1.8 (95% CI 1.4–2.2) for vismodegib. The LHH values (the ratio of the probability of benefit to the probability of harm) when treatment was discontinued due to adverse events were 1.14 for sonidegib and 0.84 for vismodegib, while when taking into account adverse events ≥ 3 degrees of severity — 1.41 for sonidegib and 0.85 for vismodegib. The NNT indicator reflects the efficacy of therapy and demonstrates how many patients need to be treated in order for one of them to achieve a clinically significant response. In this case, a lower NNT for sonidegib (1.65) indicates a higher probability of achieving a therapeutic effect compared to vismodegib (2.10). The NNH indicator characterizes the risk of adverse events leading to treatment discontinuation. The NNH values for sonidegib (1.9) and vismodegib (1.8) are close, which indicates a comparatively similar frequency of treatment discontinuations due to adverse effects. The LHH ratio integrates information about the benefit and harm of treatment, reflecting the probability of obtaining clinical benefit compared to the risk of developing adverse events. An LHH value greater than one (1.14 and 1.41 for sonidegib) indicates that sonidegib therapy is more likely to lead to a positive effect than to treatment discontinuation due to adverse events, while values below one (0.84 and 0.85 for vismodegib) indicate the opposite — the risk of harm exceeds the probability of benefit. Based on the results obtained, the authors concluded that these indicators confirm a more favorable benefit-risk profile for sonidegib compared to vismodegib. However, they conclude that the conclusions obtained require confirmation in clinical practice and/or in randomized direct comparative studies [26].

Limitations of the study

Due to the lack of direct comparative studies between the vismodegib and sonidegib, the choice of research method (justification of the research hypothesis) was carried out on the basis of our own calculations of OR and RR of disease progression in patients with laBCC receiving therapy with these medicines, 12 months after the start of treatment, and the results of testing the hypothesis about the equality of the proportions of patients with laBCC without disease progression 12 months after the start of therapy.

The study used a conservative scenario to assess the direct medical costs of systemic targeted therapy for patients with laBCC: accounting for costs only for the 1-line of therapy. The Russian Society of Clinical Oncology recommends the use of PD-1 inhibitors after disease progression while using Hedgehog inhibitors. In the 2-line of therapy, the cost of 1 administration, for example, for nivolumab, will be 205 104.24 rubles with a dosing regimen of 240 mg every 14 days and 341 840.40 rubles with a dosing regimen of 480 mg every 21 days [7] at an average price per 1 mg of 7 769.01 according to the Unified System of Cataloging of Medicines[20] and VAT of 10%. The cost of 1 month of treatment with Hedgehog inhibitors in the 1-line is 236 817.11 rubles when using vismodegib and 211 104.20 rubles in the case of using sonidegib. Reducing the risk of progression when using sonidegib in the 1st line potentially helps to reduce budget expenditures when patients with laBCC transition to the 2nd line of therapy.

Despite the objective assumptions and limitations of the study, even under a conservative assessment scenario, clinical and economic advantages of sonidegib were identified. Accumulation and analysis of real-world data on the management of patients with laBCC after progression while using Hedgehog inhibitors will allow further clarification and supplementation of the clinical and economic characteristics of sonidegib. Nevertheless, the results already obtained allow us to conclude that the medicine has a positive clinical and economic impact when used in widespread clinical practice.

CONCLUSION

Based on the results obtained in the study, the hypothesis about the clinical and economic advantages of sonidegib in the treatment of laBCC was confirmed, and data on the clinical and economic feasibility of using sonidegib in widespread clinical practice were obtained.

[20] Unified System of Cataloging of Medicines. Nivolumab. Available from: https://esklp.egisz.rosminzdrav.ru/esklp/smnn?smnn_gid=1ee6860a-bf5b-11e9-bd5d-93a13b914aa9&page=1&per_page=40

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Oksana I. Ivakhnenko — design development, collection and critical analysis of literature and regulatory legal documents, data collection and analysis, modeling and interpretation of results, writing, draft editing, final approval of the article; Vasily V. Ryazhenov — critical analysis of literature, making comments of intellectual content, draft editing; Maksim Yu. Frolov — critical analysis of literature, making comments of intellectual content, draft editing; Vladimir A. Rogov — critical analysis of literature, making comments on intellectual content, draft editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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AUTHORS

Oksana I. Ivakhnenko — Assistant of the Department of Regulatory Relations in the field of circulation of medicines and medical devices of the Sechenov First Moscow State Medical University (Sechenov University); Master of Law. ORCID ID: 0000-0002-9483-3171. E-mail: oii@hta-expert.ru

Vasily V. Ryazhenov — Doctor of Sciences (Pharmacy), Head of the Department of Regulatory Relations in the Field of Circulation of Drug Products and Medical Devices of the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-1278-5883. E-mail: 5052568@mail.ru

Maxim Yu. Frolov — Candidate of Sciences (Medicine), Assistant Professor of the Department of Pharmacology and Pharmacy of the Volgograd State Medical University. ORCID ID: 0000-0003-2679-7524. E-mail: clinpharmrussia@yandex.ru

Vladimir A. Rogov — Candidate of Sciences (Pharmacy), Senior lecturer of the Department of Pharmacy Management and Economics, Medical and Pharmaceutical Commodity Science of the Volgograd State Medical University. ORCID ID: 0000-0002-2164-2323. E-mail: varogov@volgmed.ru

REVIEW

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A comprehensive review of the pharmacological, therapeutic, and toxicological properties of boric acid and other boron-containing compounds: current landscape and future perspectives

O. Yunusoglu, I. Kalfa, M.E. Demirel, M.A. Binzet, U.Z. Sevinc, I. Turel, A.H. Kurt

Bolu Abant Izzet Baysal University
Golkoy Campus, Bolu Merkez/Bolu, Turkiye, 14030

E-mail: orucfarm@gmail.com

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The aim. In this review, information obtained through a comprehensive scan of scientific resources on recent developments in the field of health regarding boric acids and BCCs is brought together, and current and future perspectives are presented.
Matherial and methods. The literature studies on boron were collected using multiple databases (WOS, PubMed, Scopus, Science Direct, SciVerse, SciELO, Cochrane Library, Embase and Google Scholar). The health effects of boric acids and BCCs used in preclinical and clinical studies were systematically compiled.
Results and conclusion. Different natural and synthetic boron-containing compounds (BCCs) are increasingly used in the healthcare sector. To date, five BCCs drugs (bortezomib, crisaborole, ixazomib, tavaborole and vaborbactam) have been approved by the Food and Drug Administration, for diverse clinical applications. It is also understood that more than ten boron-based compounds (alabostat, sodium borocaptate, voromycin, TOL-463 and others) are being investigated in different clinical trial phases. In addition, it is seen that clinical studies are continuing for combinations of various drugs with BCCs for use in new indications. In addition, it is observed that boron and boron-containing compounds are widely used as supplements. This review also provides an overview of recent advances in the pharmacological activities of boric acids and BCCs, including antioxidant, anti-inflammatory, anti-atherosclerotic, anticancer, antimicrobial, antiparasitic, antiviral, antiprotozoal, cardioprotective, hepatoprotective, neuroprotective, osteoprotective, antidiabetic, anti-apoptotic, anti-obesity, ferroptosis properties, effects on immune system, antiepileptic, anti-Parkinson, and anti-Alzheimer's activities and the mechanisms of action involved, obtained from both *in vitro* and *in vivo* studies.

Keywords: boron-containing compounds; pharmacological profile; boron containing drugs; medical applications

Abbreviations: 4-OHFBA — 4-hydroxyphenylboronic acid; AD — Alzheimer's disease; ALT — alanine transaminase; APAP — acetaminophen; AST — aspartate transaminase; Aβ — Amyloid beta; BA — boric acid; BAD — BCL-2 associated agonist of cell death; BCCs — boron-containing compounds; BCL-2 — B-cell lymphoma 2; BIRC-2 — Baculoviral IAP repeat Containing-2; BNCT — boron neutron capture therapy; BODIPY — boron–dipyrrin; BPH — borax pentahydrate; cAMP — cyclic adenosine monophosphates; CAT — catalase; CD — cardiovascular diseases; CP — cyclophosphamide; DPPs — dipeptidyl peptidases; EMA — European Medicines Agency; FAP — fibroblast activation protein; FAS — fetal alcohol syndrome; FDA — U.S. Food and Drug Administration; GI — gastrointestinal; GPX4 — glutathione peroxidase 4; GSH — glutathione; hBNs — hexagonal boron nitride nanoparticles; HCV — hepatitis C virus; HDL-C — high-density lipoprotein cholesterol; HF — heart failure; HIV — human immunodeficiency virus; HUVEC — human umbilical vein endothelial cells; I/R — ischemia and reperfusion; IFN-γ — interferon-gamma; IL — interleukin; iNOS — inducible nitric oxide synthase; LDL — low-density lipoprotein; LPS — lipopolysaccharide; LxR-α — liver X receptor alpha; MDA — malondialdehyde; MF — myocardial fibrosis; MI — myocardial infarction; MPP+ — 1-methyl-4-phenylpyridinium; MRSA — methicillin-resistant *Staphylococcus aureus*; NaB — sodium pentaborate pentahydrate; NAD^+ — nicotinamide adenine dinucleotide; NF-κB — nuclear factor kappa B; NO — nitric oxide; OEA — oleoylethanolamide; PBCT — proton boron capture therapy; PD — Parkinson's disease; PPARγ — peroxisome proliferator-activated receptor gamma; QCT — quercetin; ROS — reactive oxygen species; SOD — superoxide dismutase; SREBP-1c — sterol regulatory element-binding protein 1c; TAC — total antioxidant capacity; TNF-α — tumor necrosis factor-alpha; OC — total oxidative status; WHO — World Health Organization.

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Комплексный обзор фармакологических, терапевтических и токсикологических свойств борной кислоты и других борсодержащих соединений: текущее состояние и будущие перспективы

О. Юнусоглу, И. Калфа, М.Э. Демирель, М.А. Бинзет, У.З. Севинч, И. Тюрель, А.Х. Курт

Университет имени Болу Абант Иззет Байсал,
14030, Турция, Болу Меркез/Болу, Кампус Байбу Гёлкёй

E-mail: orucfarm@gmail.com

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Цель. В этом обзоре собрана информация, полученная в результате комплексного изучения научных ресурсов о последних достижениях в области здравоохранения, касающихся борных кислот и БСС, а также представлены текущие и будущие перспективы.
Материалы и методы. Источники литературы были собраны с использованием нескольких баз данных (WOS, PubMed, Scopus, Science Direct, SciVerse, SciELO, Cochrane Library, Embase и Академия Google). Были систематизированы данные о воздействии на здоровье борных кислот и БСС, используемых в доклинических и клинических исследованиях.
Результаты и заключение. Различные природные и синтетические борсодержащие соединения (БСС) все чаще используются в здравоохранении. На сегодняшний день 5 препаратов БСС (бортезомиб, крисаборол, иксазомиб, тавaборол и ваборбактам) одобрены Управление по контролю качества пищевых продуктов и лекарственных средств США (FDA) для различных клинических целей. Также известно, что более 10 соединений на основе бора (алабостат, борокаптат натрия, воромицин, TOL-463 и другие) исследуются на различных этапах клинических испытаний. Кроме того, как видно, продолжаются клинические исследования комбинаций различных лекарственных средств с БСС для применения по новым показаниям. Кроме того, отмечается, что бор и борсодержащие соединения широко используются в качестве пищевых добавок. В этом обзоре также представлен анализ последних достижений в области фармакологической активности борных кислот и БСС, включая антиоксидантные, противовоспалительные, антиатеросклеротические, противоопухолевые, антимикробные, противопаразитарные, противовирусные, противопротозойные, кардиопротекторные, гепатопротекторные, нейропротекторные, остеопротекторные, противодиабетические, антиапоптотические, против ожирения, ферроптоз, влияние на иммунную систему, противоэпилептическую, антипаркинсоническую и альцгеймеровскую активность и соответствующие механизмы действия, полученные в ходе исследований как *in vitro*, так и *in vivo*.
Ключевые слова: борсодержащие соединения; фармакологический профиль; борсодержащие лекарственные средства; медицинское применение
Список сокращений: 4-OHFBA — 4-гидроксифенилбороновая кислота; АД — Болезнь Альцгеймера; АЛТ — аланинаминотрансфераза; APAP — ацетаминофен; АСТ — аспартаттрансаминаза; Aβ — бета-амилоид; БК — борная кислота; BAD — связанный с BCL2 агонист белка клеточной гибели; БСС — борсодержащие соединения; BCL-2 — белок, регулирующий уровень апоптоза в клетках; BIRC-2 — белок 2, содержащий бакуловирусный IAP; БНЗТ — бор-нейтронозахватная терапия; BODIPY — дипиррометен бора; BPH — тетраборат натрия пентагидрат; цАМФ — циклическиq аденозинмонофосфат; CAT — каталаза; ССЗ — сердечно-сосудистые заболевания; ЦФА — циклофосфамид; ДПП — дипептидилпептидаза; EMA — Европейское агентство лекарственных средств; FAP — белок активации фибробластов; ФАС — фетальный алкогольный синдром; FDA — Управление по контролю за продуктами и лекарствами США; ЖКТ — желудочно-кишечный тракт; GPx4 — глутатионпероксидаза 4; GSH — глутатион; hBN — гексагональный нитрид бора; HCV — вирус гепатита С; ЛПВП — липопротеины высокой плотности; СН — сердечная недостаточность; ВИЧ — вирус иммунодефицита человека; HUVEC — эндотелиальные клетки пупочной вены человека; I/R — ишемия и реперфузия; ИФН-γ — гамма-интерферон; ИЛ — интерлейкин; iNOS — индуцируемая синтаза оксида азота; ЛПНП — липопротеины низкой плотности; ЛПС — липополисахарид; LxR-α — альфа-Х-рецептора печени; МДА — малоновый диальдегид; МФ — фиброз миокарда; ИМ — инфаркт миокарда; $МФП^+$ — 1-метил-4-фенилпиридиний; MP3C — метициллинрезистентный золотистый стафилококк; $НАД^+$ — никотинамидадениндинуклеотид; NF-κB — ядерный фактор каппа B; NO — оксид азота; OEA — олеоилэтаноламид; ПБНЗТ — протонно-бор-нейтронозахватная терапия; БП — болезнь Паркинсона; PPARγ — рецептор, активируемый пероксисомным пролифератором гамма; QCT — кверцетин; АФК — активные формы кислорода; СОД — супероксиддисмутаза; SREBP-1c — белок, связывающий регуляторный элемент стерола 1; ТАС — общий антиоксидантный статус; TNF-α — фактор некроза опухоли альфа; ОС — общий окислительный статус; ВОЗ — Всемирная организация здравоохранения.

INTRODUCTION

Boron is a naturally occurring trace element found in both the environment and living systems, where it plays diverse roles in numerous biological processes [1]. It is distributed in the Earth's crust, soil, and oceans, existing at specific concentrations. The average boron concentration in soil is 10–20 ppm [2]. Boron is found in various regions of the world, particularly in countries like the United States, Turkey, Brazil, Russia, and China, which have substantial boron reserves [3, 4]. By taking part in hydroxylation processes, boron plays a crucial function in the production and metabolism

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of several reactions [5, 6]. Primarily, at the neutral pH levels present in most biological fluids, boron exists as boric acid (BA; H_3BO_3) and a small amount of borate anion ($B(OH)_4^-$). Both BA and borate tend to form complexes with sugars and other compounds containing trans-hydroxyl groups [7]. Boron compounds are known to be water-soluble. Both borax and BA are soluble in water, and it is well-known that the solubility of BA in water increases with rising temperatures [8].

Organoboron compounds are one of the most versatile classes of heteroatom-containing organic molecules [9]. This versatility is due to the unique chemical properties of boron. In analytical chemistry, the slightly Lewis acidic character of the boron atom is particularly valued in areas such as carbohydrate and fluoride determination [9]. This property plays an important role in analytical processes thanks to its ability to form tetracoordinate borates with fluoride anions and polyols [10, 11]. Boron is more electropositive than carbon, and this fundamental property is most efficiently utilized in organic synthesis, which has become one of the most important application areas of organoboron compounds [9]. This property of boron allows catalytic effects and selective reactions in various organic transformations. Given the covalent binding capacity of boron to biological targets, it can be assumed that organoboron compounds are simple electrophiles, similar to acrylates, epoxides and aldehydes, which are known electrophilic agents of chemical biology [12]. However, the behaviour of boron in biological systems is more complex, making it a unique chemical tool. According to studies, boron has the ability to form multiple covalent bonds with a protein, although boronic acids hydrate in aqueous solution and in some examples, boron was observed to interact indirectly with histidine via a bridging water molecule [13]. This feature enables boron to offer a unique binding mechanism in biological systems. Boron and its compounds are also used to develop methods for drug analysis [14–16] and to modulate different chemical reactions [17–19]. The role of boron compounds in chemical biology and drug discovery is increasing. The unique chemical properties, selective binding mechanisms and low toxicity of boron make it a valuable element in the development of therapeutic agents.

Boron concentrations vary between species, and low boron levels inhibit growth [20–22]. Recognized as a trace element, boron has low toxicity in mammals and is essential for the development of animals and human bodies [23, 24]. Additionally, optimal boron intake is suggested to positively influence bone growth and development [25, 26], the proliferation and differentiation of blood cells, and brain functions [27–29]. However, it has also been reported that excessive intake of boron can be harmful [30, 31]. Experimental boron applications in animals and humans have been shown to result in significant improvements in immunity, antioxidant effects, growth, and embryonic development [1]. Natural boron compounds possess antibacterial, antiviral, and anticancer properties [32, 33]. Boron is necessary for a wide range of metabolic processes in microorganisms, including antibiotic action, nitrogen fixation, and quorum sensing [34]. Furthermore, thanks to their anti-inflammatory properties, these compounds are used as dietary supplements for the treatment of neuroinflammation and neurodegeneration [35]. Approximately 80% of the global population use conventional medicine for healthcare [36]. In individuals with boron deficiency, reductions in high-frequency brain activity have been associated with memory impairment [37–39]. Borax, one of the boron compounds, exhibits antiseptic, antifungal, and antiviral effects, as well as anti-osteoporotic, anti-inflammatory, hypoglycemic, and anticoagulant properties [40, 41]. Because of its ability to scavenge free radicals, it has also been reported to have antioxidant qualities. It inhibits proliferation in tumor cells and shows anticancer effects by inducing apoptosis [42–44]. BA has also been reported in numerous studies to have antioxidant [45], anti-genotoxic [46], anti-carcinogenic [47], non-cytotoxic [48], and metal-chelating properties [49, 50]. Boron-containing compounds (BCCs) have a wide range of pharmacological activities (Fig. 1).

Currently, medicinal chemists are investigating boron-based small compounds due to the Lewis acid characteristics of boron, which render it reactive towards the nucleophiles found in enzymes, nucleic acids, and carbohydrates [51]. Recently, the U.S. Food and Drug Administration (FDA) sanctioned three BCCs: two from the BA category and one from the

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benzoxazole category [51, 52]. Boronic acids serve as transition state analogs for enzymes such as proteases and lactamases, so efficiently suppressing their function. Boron has garnered considerable interest owing to the FDA approval of multiple boron-containing pharmaceuticals and the existence of additional related pharmacological compounds undergoing clinical testing [6, 51]. It has received significant attention due to FDA approval of multiple boron-containing drugs and the existence of additional related pharmacological compounds undergoing clinical testing [51, 52]. Information was obtained from the European Medicines Agency (EMA), the FDA website, the DrugBank database and various scientific sources. Boron-containing drugs that have received FDA approval to date are shown in Table 1.

In addition to the above drugs that have received FDA approval, various boron and its compounds are being investigated in clinical studies (phases 1 to 3). Among the molecules that have received FDA approval, clinical phase studies continue for GSK8175/GSK2878175 molecule in hepatitis C virus (HCV) clinical research, ganfeborole hydrochloride/(GSK656) molecule in tuberculosis research, xeruborbactam/(QPX7728) molecule as an antibacterial, and AN-2898 molecule in topical dermatitis. Several BCCs are currently undergoing clinical trials, exploring their potential therapeutic applications across various medical fields. Table 2 below provides a detailed summary of these compounds.

Numerous BCCs have been studied, acknowledged for their advantageous qualities, and distributed internationally [1, 69, 70]. BA, borinic acids, and their derivatives, such as borinates, oxoboranes, and boronic acid derivatives, serve as enzyme inhibitors and regulate the opening and closing of membrane ion channels [71]. Research demonstrates that boron, alongside oxygen, was essential in the first synthesis of RNA molecules on Earth [72]. Due to its pronounced electrophilic characteristics, boron and its derivatives have been incorporated into various therapeutic candidates, leading to considerable study in recent years on the synthesis of innovative boron-based structures [73–75]. Historically, the pharmaceutical use of boron was primarily limited to antiseptics; however, its therapeutic range has broadened in recent decades to encompass antibiotics and anticancer drugs [76–78]. A notable characteristic of the boron atom is its ability to absorb neutrons, which has facilitated the advancement of many drug discovery platforms [79]. Furthermore, the documentation of newly synthesized boron-based chemicals affecting metabolic processes in both animals and humans is increasing [80]. The chemical structures of some boron compounds are presented in Table 3.

Boron is known to play a role in growth due to its ability to strengthen cell membranes [81]. It is essential for plant growth and development, contributing to healthy growth and productivity in plants [82]. Approximately 90% of boron in plant cells has been estimated to reside in the cell walls [81]. Boron can form complexes with compounds such as polyhydroxyl polymers, pectins, and polyols, which are components of the cell wall [82, 83]. Thus, by forming esters with cis-diol components of the cell wall, boron aids in stabilizing and synthesizing the cell wall, providing shape, strength, and rigidity to the cell [1, 81]. Plants are also known to be impacted by BA, which is usually found in their cell walls [7, 84–86]. To fully grasp the potential of boron in medicinal chemistry, more research is necessary, as demonstrated by the drug analogs that exhibit a range of biological activities with a single boron atom or boron cluster molecules. This study will highlight many of the uses of boron chemistry in the medical profession, however there have been other reviews and books recently that demonstrate the advancements in boron chemistry and its applications.

THE AIM. This review aims to provide a comprehensive overview of the expanding role of BA and BCCs in the healthcare field. In recent years, both natural and synthetic BCCs have garnered significant attention due to their diverse pharmacological properties and growing clinical relevance. Several BCCs have already received regulatory approval for medical use, while many others are currently undergoing various phases of clinical evaluation. In addition, new therapeutic strategies involving the combination of BCCs with other pharmaceutical agents are being actively explored. This review focuses on the broad spectrum of biological activities exhibited by BA and BCCs, including antioxidant, anti-inflammatory, anticancer, antimicrobial, antiviral, antiparasitic, neuroprotective, cardioprotective, hepatoprotective, osteoprotective,

and antidiabetic effects. The mechanisms of action underlying these activities, as demonstrated in both *in vitro* and *in vivo* studies, are discussed in detail. Furthermore, the review highlights the use of boron-based compounds as dietary supplements and examines their potential contributions to human health. Scientific data were systematically collected from multiple reputable databases, including Web of Science, PubMed, Scopus, ScienceDirect, SciVerse, SciELO, Cochrane Library, Embase and Google Scholar. Overall, this review aims to synthesize recent advancements, evaluate current applications, and provide insights into future directions for the use of BA and BCCs in medical and therapeutic contexts.

MATERIALS AND METHODS

This systematic review was conducted in accordance with PRISMA guidelines and was registered in the International Prospective Register of Systematic Reviews. A literature search was carried out across multiple electronic databases PubMed, Web of Science, Scopus, Google Scholar, Cochrane Library, and Embase to identify relevant studies published in English, with no time restrictions. The search terms were designed to align with the research objectives, using Boolean combinations such as: “pharmacokinetics,” “pharmacodynamics,” “bioavailability,” “therapeutic potential,” “biological activity,” “pharmacological activity,” “antimicrobial activity,” “clinical trial,” “toxicity,” and other terms related to “boric acid” or “boron-containing compounds/BCCs”. A systematic search conducted across multiple scientific databases yielded a total of 312 eligible studies (n = 312), comprising both original research articles and review papers, which were subsequently included in the present analysis.

RESULTS AND DISCUSSION

The pharmacokinetic properties of boric acid and boron-containing compounds

Absorption of boric acid and boron-containing compounds

Humans have good absorption of boron from the gastrointestinal (GI) tract [87]. Research has indicated that around 90% of boron ingested orally is absorbed by both humans and animals [87]. According to the World Health Organization (WHO), humans absorb 0.44 μg of boron per day through their inhaled air, 1.2 mg per day on average through their diet, and 0.1–0.3 mg per liter of boron through their drinking water [88]. Vanderpool et al (1994), the GI tract absorbs more than 90% of boron taken orally in 3 hours, and the absorption is finished in 24 hours [89]. Furthermore, absorption through the skin is one of the ways BA enters the body. Although studies have shown that the passage through intact skin is low, it is stated that absorption may increase in the presence of damaged skin [90].

Distribution of boric acid and boron-containing compounds

BA is found in large quantities in bodily water in humans (98.4% as BA and 1.6% as the, $B(OH)_4$) [91]. The distribution of BA in humans and animals is comparable. Not all BCCs can reach the entire organism, even those with a significant volume of dissemination [92]. This implies that certain barriers contain transporters. Additionally, following BA treatment, bone boron levels seem to be higher than those in plasma or soft tissues, while boron levels in soft tissues are equal to those in plasma [93]. Furthermore, it has also been shown that some boron-containing nanoparticles and BCCs tend to preferentially accumulate in specific organs, such as the brain or heart [94].

Metabolism of and biotransformation of boric acid and boron-containing compounds

In both humans and animals, BA is not metabolized. Because breaking the B-O bond requires a lot of energy (523 kJ/mol), biological systems are unable to metabolize BA. Many inorganic borates are metabolized at low concentrations, despite the fact that BA is not. And also, they produce BA as the primary metabolite at physiological pH on mucosal surfaces prior to absorption [93]. Additionally, it is known that BCCs can undergo biotransformation, and that this biotransformation frequently involves boron-free bonds, even though there are no known enzyme processes that break boron-containing bonds [95].

Elimination and excretion of boric acid and boron-containing compounds

According to the statistics, hepatic and renal clearance are the main factors influencing boron

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excretion [95]. Boron is mostly expelled through urine, with only trace amounts seen in perspiration, breath, and bile, and to a lesser degree through stool (2%) [96]. Studies show that the amount of fecal and urine excretion increased along with the dietary intake of boron [1]. Despite having fairly similar renal clearance values (39 and 55 mL/min/1.73 m^2 in humans; 40 mL/min/1.73 m^2 in mice), rats and mice typically have higher rates of renal clearance than humans, which suggests the possibility of different mechanisms at play [97]. Six volunteers were given roughly 131 mg of BA in water (750 mg) and water-emulsifying ointment (740–1473 mg, or roughly 130–258 mg BA) by WHO (2009) and they discovered that, on average, 92–94% of the BA that was given was eliminated in the urine after 96 hours [98].

Therapeutic potential and biological activities of boric acid and boron-containing compounds

Anti-inflammatory activity of boric acid and boron-containing compounds

Inflammation serves as an initial defense mechanism against harming agents, notably toxins, pathogens, and allergens [99]. When the acute inflammatory response persists, the immune system engages in a more intricate, prolonged reaction. The chronic inflammatory response is typically of low intensity and encompasses numerous proinflammatory cellular elements, including leukocytes predominantly consisting of macrophages and lymphocytes. Due to their effectiveness in alleviating pain and inflammation, nonsteroidal anti-inflammatory drugs rank among the most utilized medications, solidifying their status in the WHO Model List of Essential Medicines [100]. Non-steroidal anti-inflammatory medicines account for 30% of hospital admissions due to preventable adverse drug reactions, primarily resulting in bleeding, myocardial infarction (MI), cerebrovascular accident, and renal impairment [101]. According to the research, it investigated the potential of BA as a novel anti-inflammatory medication [102–105]. Anti-inflammatory effects of BA have been demonstrated *in vitro* [106–109] and *in vivo* [110–112]. The effects of BA on anti-inflammatory parameters are presented schematically in Figure 2. A study by Gundogdu et al (2024), BA has shown potential effectiveness in decreasing inflammation in a rat model of knee osteoarthritis [113]. Tekeli et al (2022) study that supplementing with BA regulates the inflammatory alterations associated with ovariectomy [114]. Moreover, Cao et al (2008) demonstrated that BA was proven to possess strong anti-inflammatory action through the inhibition of the nuclear factor kappa B (NF-κB) signaling pathway and possesses therapeutic potential, especially in chronic inflammatory diseases such as rheumatoid arthritis [102]. In that study, it was shown that the BA significantly decreased the expression of pro-inflammatory cytokines, suppressed inflammatory cell infiltration and that its effect on tumor necrosis factor-alpha (TNF-α) secretion could be induced via thiol-dependent mechanism [102].

Anticancer activity of boric acid and boron-containing compounds

Anticancer activity denotes the capacity of chemicals to impede the growth and multiplication of cancer cells or to trigger their apoptosis [115, 116]. Numerous epidemiological and experimental investigations have shown that BA may have anti-cancer effects on a range of cancer types. Given the lack of definitive treatment for all the different types of cancers, these studies looked into the potential of this substance as a novel therapeutic option for alleviating symptoms and slowing disease progression. Series of recent studies showed effect of BA on hepatocellular carcinoma, endometrial and ovarian cancer, colon cancer, lung cancer, prostate cancer, breast cancer, glioblastoma and thyroid cancer [117–120]. The cytotoxic role of BA application on glioblastoma treatment was investigated by Aydin et al (2021). It was observed that high-dose BA applications had a fatal effect on glioblastoma cells, but non-toxic dosages of BA application did not inhibit proliferation of these cells. As a result of their study, high dosage of BA solution application has been found to be a promising strategy for treating glioblastoma [121]. Furthermore, Lin et al (2013) demonstrated that rats with hepatocellular carcinoma treated with boron neutron capture treatment seemed to have smaller tumors on ultrasound images and clearly had less blood flow to the tumor. On the 80th day following boron neutron capture treatment, the liver lesion had vanished;

a recovery of values to normal levels was also observed [122].

BA and borax dramatically decreased U-87MG cell viability in a concentration-dependent manner, according to Turkez et al (2021). Moreover, they discovered that whereas boron compounds improved the activities of the superoxide dismutase (SOD) and catalase (CAT) enzymes and raised malondialdehyde (MDA) levels and total oxidative status (TOS), they simultaneously decreased glutathione (GSH) levels and total antioxidant capacity (TAC) [123]. In studies examining the effects of BA on breast cancer cell lines (MCF-7 and MDA-MB-231), BA was found to inhibit the growth of breast cancer cells in both 2D and 3D culture media [120]. Furthermore, BA and calcium fructoborate were reported to inhibit cell proliferation in MDA-MB-231 cancer cell lines [124]. BA is also thought to exert a mechanism of action by partially influencing the DNA damage response in breast cancer cells [125]. Based on these findings, studies on breast cancer and BA suggest that BA could be proposed as a chemical protective agent [126, 127]. Besides, the mechanisms of induction of apoptosis by boron against cancer cells are multilevel. Boron induces mitochondrial membrane permeability due to DNA damage, which triggers apoptosis [112, 115, 117, 128]. During the process, the pro-apoptotic proteins BAX, BAK, CASP-3, and B-cell lymphoma 2 (BCL-2) associated agonist of cell death (BAD) were upregulated, and anti-apoptotic genes like baculoviral IAP repeat containing-2 (BIRC-2), BIRC-5, and BCL-2 were downregulated. Additionally, cell cycle arrest was induced by boron in the G2/M and Sub-G1 phases, inhibiting the proliferation of cancer cells [112, 115, 117, 128]. These findings were further supported by detection methods such as ELISA, western blot, and flow cytometry, hence positioning boron as one of the promising candidates in cancer therapies. Further studies are needed to confirm the selectivity of the anticancer effects of boron (Fig. 3).

Activity of boric acid
and boron-containing compounds on apoptosis

Apoptosis functions as a critical physiological mechanism that controls cell population expansion, either to preserve tissue homeostasis or to clear potentially hazardous cells, such as those that suffered DNA damage. In cancer, cell-autonomous apoptosis is a prevalent tumor suppressor mechanism, which is utilized in cancer therapy [129]. Currently, research is investigating the potential of boron compounds as a new anti-apoptotic drug. A study by Hilal et al (2024) has provided evidence for BA induced apoptosis by downregulation of anti-apoptotic genes and upregulation of pro-apoptotic genes [130]. In their study, Cengiz et al (2019) investigated the toxicity induced by cyclophosphamide (CP) exposure in rat livers and the potential protective effects of BA. In contrast to the CP group, TAC marker levels increased while alanine transaminase (ALT), aspartate transaminase (AST), alkalen phosphatase (ALP), TOS, oxidative stress markers, and caspase-3 levels reduced in the BA and CP group. These results demonstrated that BA effectively shielded the liver against CP-induced apoptosis and histological alterations [131].

Boron neutron captures therapy on cancer activity

Boron neutron capture therapy (BNCT), a new treatment approach intended to improve the therapeutic ratio for malignancies that have historically been difficult to cure, is the main biological use of boron-based compounds [132–134]. By carefully concentrating boron compounds within tumor cells and then exposing them to epithermal neutron beam radiation, which specifically kills the tumor cells, BNCT is showing promise as a cancer treatment method. The ability of BNCT to deposit a significant dosage gradient between tumor cells and healthy cells is one of its special qualities. The most advantageous characteristics of boron compounds are there is minimal systemic toxicity, strong tumor absorption in normal tissues, significant tumor/brain and tumor/blood concentration ratios (>3–4:1), tumor concentrations of 20–35 mg ^{10}B/g tumor, quick removal from blood and normal tissues, and tumor persistence during BNCT [135, 136]. The most common methods for delivering boron are boronophenylalanine and sodium borocaptate [137]. The basis for BNCT treatment is nuclear capture and fission when nonradioactive boron-10 is irradiated with low thermal neutrons (<0.025 eV), which produces a recoiling lithium-7 ($^{10}B_5 + {}^1n_{0(th)} \rightarrow [{}^{11}B_5]^* \rightarrow {}^4He_2(\alpha) + {}^7Li_3 + 2.38$ MeV) and an alpha particle. A type of high linear energy transfer particle known as an alpha particle deposits energy over a distance of less than 10 μm, or around one cell›s diameter [135, 137, 138]. The mechanism of BNCT in the tumor cell is shown in Figure 4.

Head and neck cancer, Glioblastoma multiforme,

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recurrent lung cancer, squamous cell carcinomas, salivary gland carcinomas, sarcomas, recurrent malignant meningioma, multifocal hepatocellular carcinoma and extramammary Paget's disease are among the cancers that BNCT has been used to treat thus far [139–141].

Proton boron capture therapy on cancer activity

Proton boron capture therapy (PBCT) is a new treatment strategy that uses protons to create a physical-driven radiosensitization. By taking use of a nuclear fusion reaction between low-energy protons and ^{11}B atoms, $p + {}^{11}B \rightarrow 3\alpha$ (p-B), it increases the biological efficacy of protons by releasing α-particles that are thought to cause double-strand breaks in DNA across Spread-Out Bragg Peak [142]. This method makes it possible to limit the radiosensitization to the object that the proton beam strikes [143]. Alpha particles with energies between 2 and 5 MeV release almost all of the energy of the nuclear process. These alpha particles harm cells close to the reaction site because of their short linear travel and strong linear energy transfer inside the tissue. By selecting the boron compounds that are preferentially deposited inside the tumor, it is possible to optimize the dosage in the tumor location and limit it outside [144]. There are *in-vitro* studies to evaluate the effectiveness of PBCT on cancer. For this, the inclusion of boron in the U-87 MG glioblastoma cell line and the DU145 prostate cancer cell line is known to decrease cell survival by a factor of 2 following proton irradiation in the PBCT experiments [143, 145–147].

Anticancer activity of boron-dipyrromethene

Thanks to their special photophysical characteristics and functionalization potential, near-infrared boron–dipyrrin (BODIPY) and their analogs have been the subject of much research [148]. BODIPY derivatives are widely used in the biomedical field, especially in biological imaging and photodynamic therapy applications due to their high photostability, strong fluorescence properties and wide absorption-emission ranges [149–152]. In recent years, the importance of fluorescent dyes in biological imaging and sensor applications has been increasing [151]. In this case, BODIPYs stand out with their superior photophysical properties compared to other fluorescent dyes, such as narrow absorption and emission bands, high fluorescence intensity and simple signal modulation for practical applications [152]. Owing to these properties, BODIPYs are widely used in areas such as cell imaging, biosensor design and photodynamic therapy [153]. These compounds, whose photophysical properties can be optimised by structural modifications, can be used as targeted diagnostic agents and offer significant advantages especially in the specific detection of cancer cells [151, 152]. Jang et al (2019) developed a BODIPY platform activated by 365 nm UV light. This system shows promise for targeted therapy and imaging by simultaneously providing both anticancer drug release and 'lighten-up' FLI [154]. In another study, Wang et al (2019) developed an innovative therapeutic and diagnostic platform comprising an H_2S-sensitive NIR probe (NIR-BSO) and a potent photosensitiser (3I-BODIPY) for accurate cancer imaging and on-demand image-guided photodynamic therapy [155].

BODIPY-based theranostic agents have a wide range of uses in the biomedical field for both diagnostic and therapeutic purposes. It allows deep tissue analysis with photoacoustic imaging, monitoring of cellular biomarkers with fluorescence imaging, and can target cancer cells by activating with light through photothermal and photodynamic therapies [156]. It can also be used as a drug carrier in chemotherapy, providing controlled release and monitoring tissue temperature with photothermal imaging. Thanks to these versatile properties, BODIPY derivatives are promising agents for advanced biomedical research and cancer treatments.

Effect of boric acid and boron-containing compounds on cell death via ferroptosis

Ferroptosis is a non-apoptotic iron-dependent form of programmed cell death. It is morphologically, biochemically and genetically different from other types of programmed cell death such as apoptosis, necrosis and autophagy. The effects of boron on ferroptosis have recently attracted attention. Ferroptosis leads to damage to the mitochondrial membrane and destruction of mitochondrion crystals. This disrupts the energy production of the cell and triggers cell death [157]. However, iron is involved in the process of lipid peroxidation, which leads to oxidation of intracellular lipids and cell death [158]. In addition, proteins that regulate iron metabolism (e.g. IRP [Iron Regulatory Protein] и IRE [Iron Response Element]) may cause a disturbance of iron balance, which may contribute to the occurrence of ferroptosis [159].

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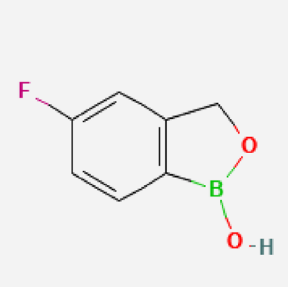
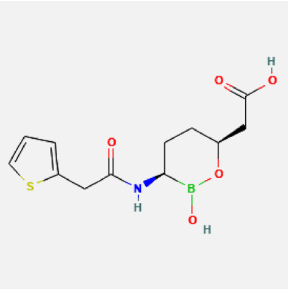
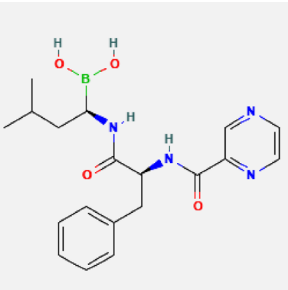
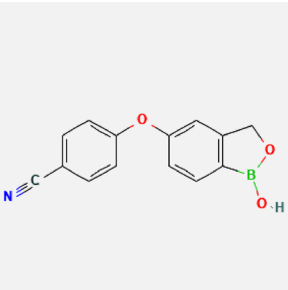
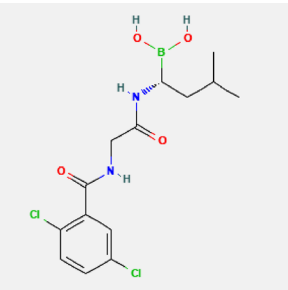
Table 1 – Molecular Architectures and clinical applications of FDA-approved boron-containing drugs

Drug Name / FDA Approed Date	Indications	Mechanism of action	Chemical structure	References
Tavaborole / July 7, 2014	Fungal or yeast infections of the toenails	It inhibits cytosolic leucyl-transfer RNA synthetase which plays a key role in fungal essential protein synthesis		[53]
Vaborbactam / August 29, 2017	Urinary tract infections	Non-β-lactam β-lactamase inhibitor		[54]
Bortezomib / May 13, 2003	Multiple myeloma	Reversibly binds to the chymotrypsin-like subunit of the 26S proteasome, resulting in its inhibition and preventing the degradation of various pro-apoptotic factors		[55]
Crisaborole / December 14, 2016	Atopic dermatitis (eczema)	Broad-spectrum anti-inflammatory activity by mainly targeting PDE4 enzyme that is a key regulator of inflammatory cytokine production		[56]
Ixazomib (Citrate) / November 20, 2015	Multiple myeloma	Blocks protein degradation by inhibiting the 20S catalytic subunit of the 26S proteasome		[57]

Note: The images of the chemical structures are taken from PubChem. PDE4 — phosphodiesterase 4.

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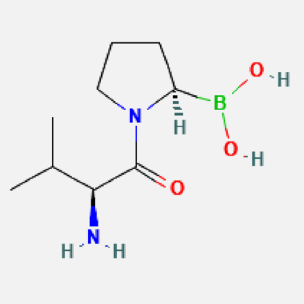
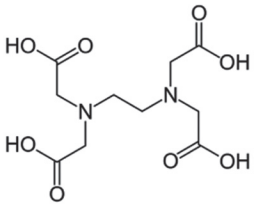
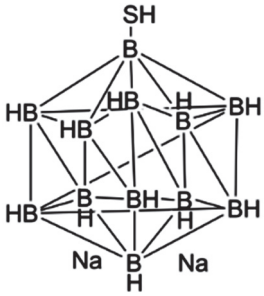
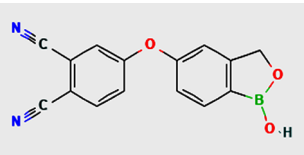
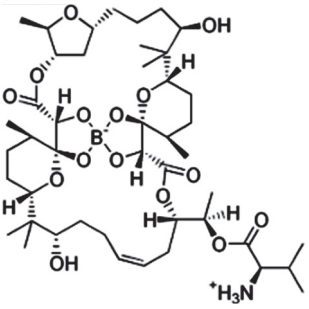
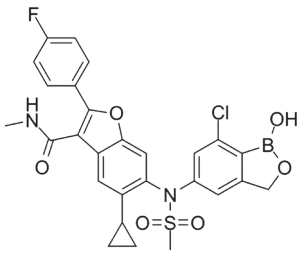
Table 2 – Boron-containing compounds evaluated in clinical trials (phases I–III)

Chemical Name	Indications	Mechanism of Action	Chemical Structure	References
Talabostat (PT-100)	Non-small-cell lung cancer and malignant melanoma	Inhibits tumor-associated FAP and DPPs		[58]
TOL-463	Bacterial Vaginosis and Vulvovaginal Candidiasis	Targeting vaginal bacterial and fungal biofilms		[59]
Sodium Borocaptate	Glioblastoma multiforme	When the blood-brain barrier is disrupted, it penetrates into the brain and affects the cells.		[60]
AN-2898	Atopic dermatitis	3',5'-cyclic-AMP phosphodiesterase (4A-4B-4D) inhibitor		[61]
Boromycin	Gram-positive bacterial infections, coccidiosis, and protozoal infections	Negatively affecting the cytoplasmic membrane, resulting in the loss of potassium ions from the cell		[62]
GSK8175/ GSK2878175	Anti-hepatitis C virus	NS5B inhibitor		[63]

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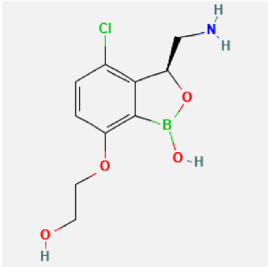
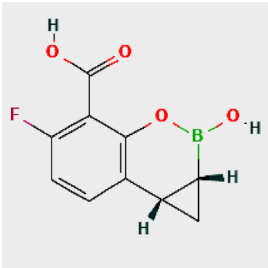
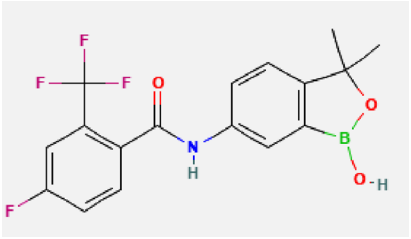
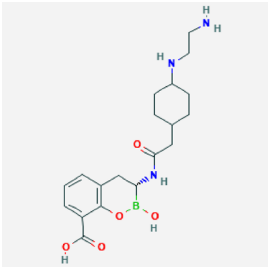
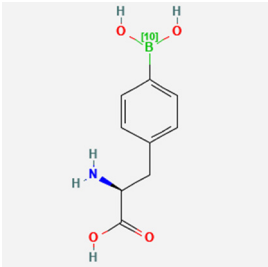
Chemical Name	Indications	Mechanism of Action	Chemical Structure	References
Ganfeborole/ (GSK656)	Anti Tuberculosis agent	Ganfeborole is a first-in-class benzoxaborole inhibiting the Mycobacterium tuberculosis leucyl-tRNA synthetase.		[64]
Xeruborbactam/ (QPX7728)	Ultra-broad-antibacterial spectrum	Beta-lactamase inhibitor		[65]
Acoziborole	African trypanosomiasis	Specifically block the active site and mRNA processing by parasite, but not host CPSF3		[66]
Taniborbactam	Acute pyelonephritis	Reversible, covalent inhibitor of serine β-lactamases and as a competitive inhibitor of metallo-β-lactamase		[67]
Borofalan	Malignant Glioma	Molecular selectivity towards the targeted tumor cell, the nucleus or DNA is targeted		[68]

Note: The images of the chemical structures are taken from PubChem. FAP — fibroblast activation protein-α; DPPs — dipeptidyl peptidases; NS5B — non-nucleoside polymerase.

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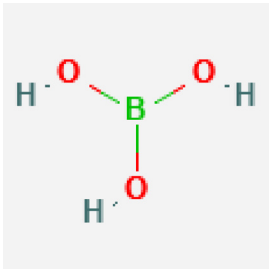
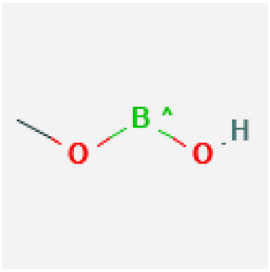
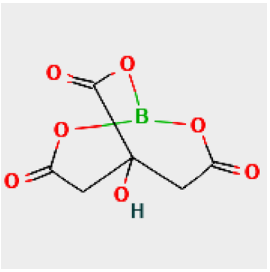
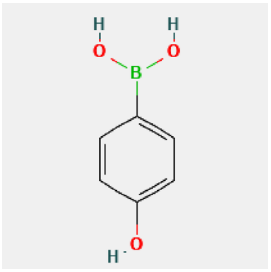
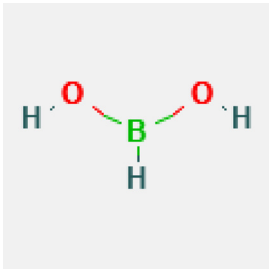
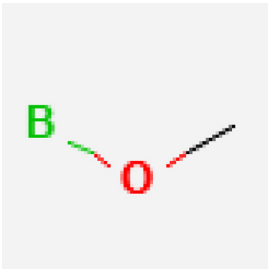
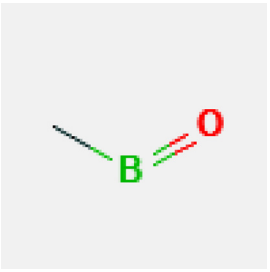
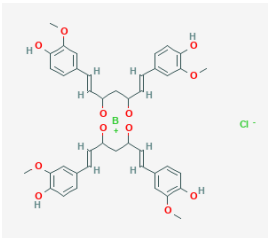
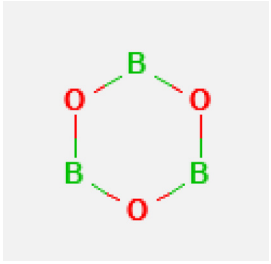
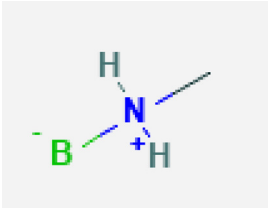
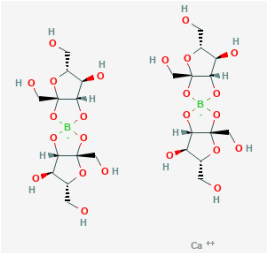
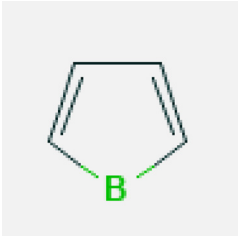
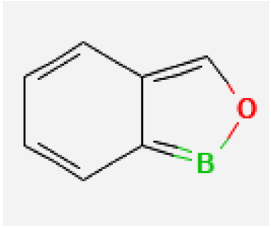
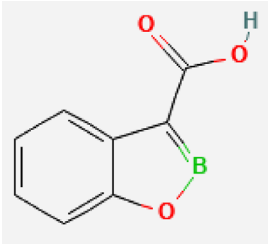
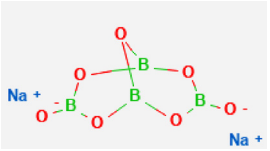
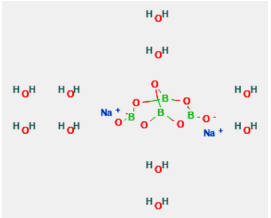
Table 3 – The chemical structure of some boron compounds

 Boric Acid	 Boronic Acid Methyl Ester	 Boron Citrate	 4-Hydroxyphenylboronic acid (4-OHFBA)
 Boronic Acid	 Borinic acid, methyl ester	 (Methyl)oxoborane	 Rosocyanine
 Boroxine	 (Methyl)amine borane	 Calcium Fructoborate	 Borole
 Benzoboroxole	 Carboxy-benzoxaborole	 Borax	 Sodium Tetraborate Decahydrate

Note: The images of the chemical structures are taken from PubChem.

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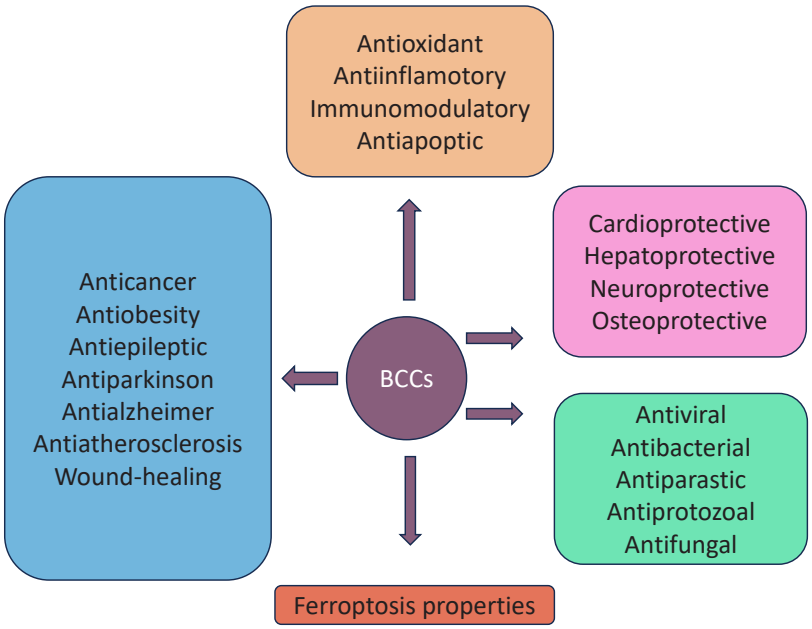

Figure 1 – Pharmacological and therapeutic potential of boron-containing compounds.
Note: The figure was created using Microsoft Office software. BCCs — boron-containing compounds.

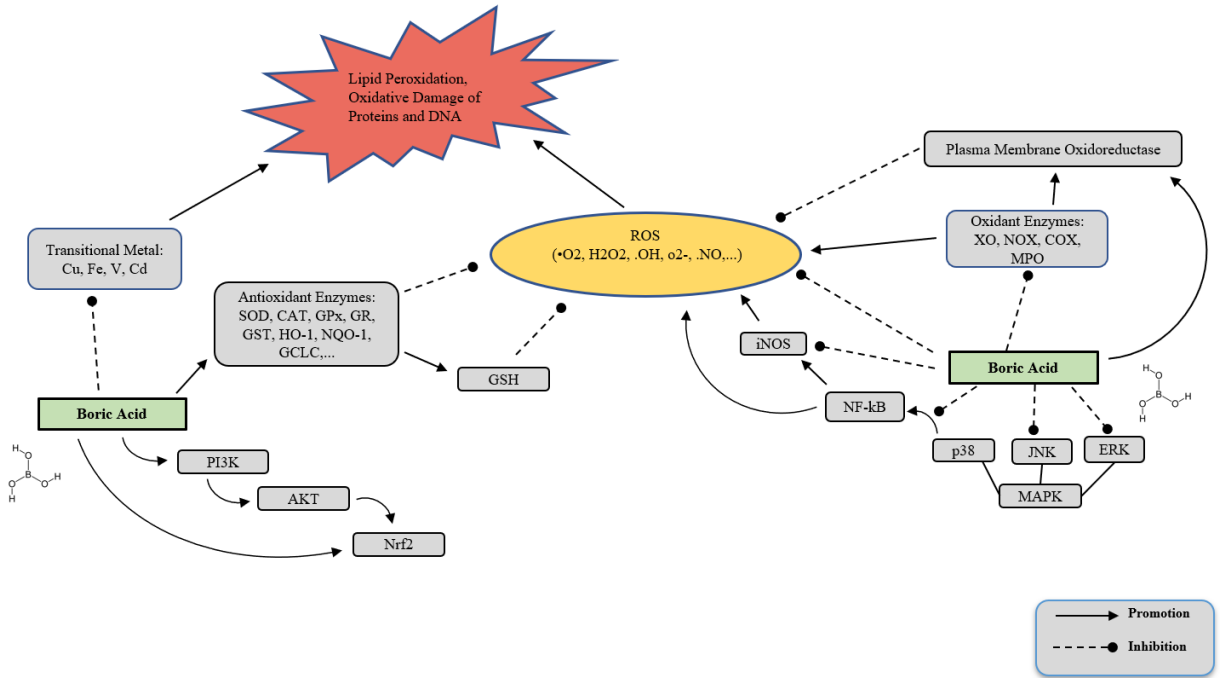

Figure 2 – Effects of boric acid on various anti-inflammatory parameters.
Note: The figure was created using Microsoft Office software. Akt — Protein Kinase B; CAT — Catalase; COX — Cytochrome c Oxidase; CLC — Glutamate Cysteine Ligase ERK — Extracellular Signal-Regulated Kinases; GSH — Reduced Glutathione; GPx — Glutathione Peroxidase; GR — Glutathione Reductase; GST — Glutathione S-Transferases; HO-1 — Heme oxygenase 1; iNOS — Inducible Nitric Oxide Synthase; JNK — c-Jun N-terminal kinase. MAPK — Mitogen-Activated Protein Kinase; PI3K — phosphatidylinositol-3-kinase; MPO — Myeloperoxidase; NF-κB — Nuclear Factor kappa B; Nrf2 — Nuclear Erythroid 2-related Factor 2; NOX — oxidase; NQO-1 — Quinone Oxidoreductase; ROS — reactive oxygen species; XO — xanthine oxidase; SOD — superoxide dismutase.

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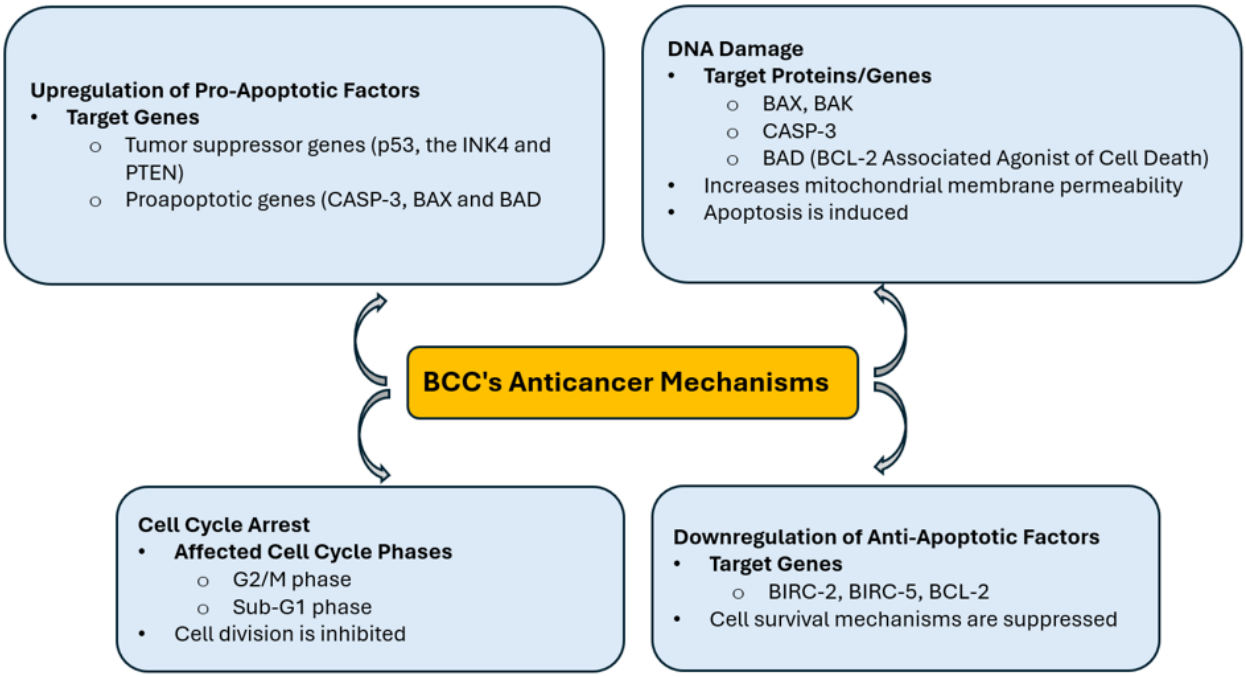

Figure 3 – Molecular base anticancer mechanism of boron-containing compounds.
Note: The figure was created using Microsoft Office software.

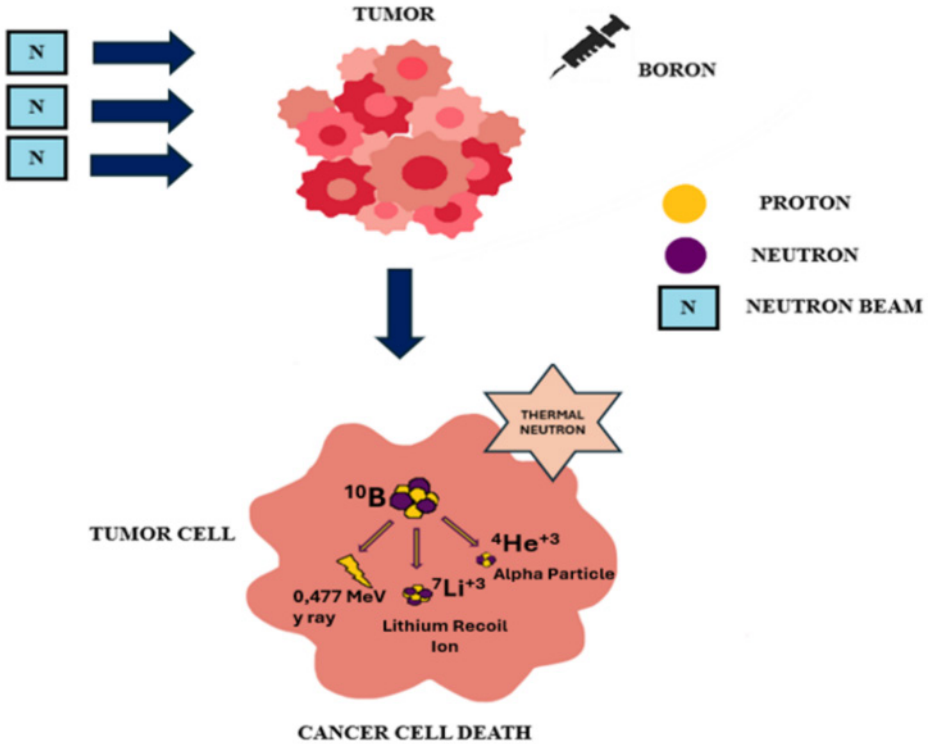

Figure 4 – Tumor cells that are treated with thermal neutrons preferentially contain injected boron compounds.
Note: After that, the boron reacts to producing an inert lithium ion and an alpha particle. The tumor cell is then harmed by the alpha particle within a limited range. The figure was created using Microsoft Office software.

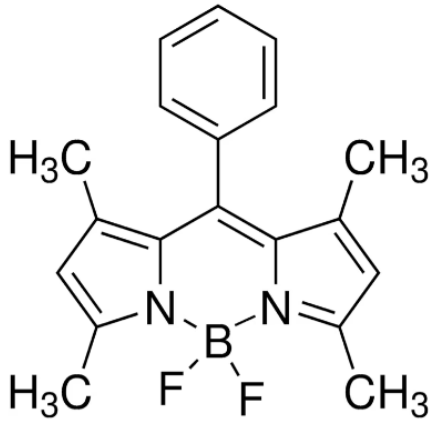

Figure 5 – Near-infrared boron–dipyrrin (BODIPY)

Although data on the effects of boron on ferroptosis are limited, the antioxidant properties of boron and its potential regulatory effects on iron metabolism suggest that these two processes may be related [157, 158, 160]. Boron, especially in the form of BA, has been shown to affect ferroptosis pathways. BA is the predominant form of boron in plasma. Boron has been identified as a potential modulator of ferroptosis, a regulated form of cell death characterized by iron-dependent lipid peroxidation [161]. The effects of boron on ferroptosis are particularly important in the context of cancer therapy, where induction of ferroptosis may overcome resistance to conventional therapies, suggesting its potential as a therapeutic agent in cancer treatment [162, 163]. BA has been shown to induce ferroptosis in glioblastoma cells by affecting the semaphorin-neuropilin signaling pathway [163]. This induction is dose-dependent and is associated with increased levels of total oxidant molecules and caspase proteins, which are markers of cell death. BA disrupts the SEMA3F pathway, leading to decreased cell proliferation and increased apoptosis in tumour cells [163]. Induction of ferroptosis by boron is mediated by modulation of key ferroptosis markers such as glutathione peroxidase 4 (GPx4) and ACSL4. These markers are very important in maintaining the redox balance in cells and their disruption leads to increased lipid peroxidation and cell death [161, 163].

The use of boron in combination with other ferroptosis inducers such as nanoparticles may further increase therapeutic efficacy. Nanoparticles can increase their concentrations in tumor tissues and reduce systemic toxicity at lower doses in the administration of ferroptosis-inducing agents [164–166]. Considering that cancer cells may be more vulnerable to agents that disrupt redox balance and increase oxidative stress, high concentrations of BA may be more harmful to tumor cells through modulation of energy production [167, 168]. In this perspective, BA and boronates can be used as chemosensitising agents to induce/enhance ferroptosis [169]. However, boron may also play a role in the regulation of ferroptosis by cross-linking with other ions such as iron ions. This cross interaction may further contribute to the induction of ferroptosis in cancer cells by affecting oxidative stress and lipid peroxidation [170]. It has also been shown that boron dissociates phosphorus in iron alloys. This suggests that boron may modulate iron metabolism, an important component of ferroptosis, and cell death by altering the availability and distribution of iron within cells [166, 168]. In conclusion, while boron shows promise in modulating ferroptosis and improving cancer therapy, it is important to consider ferroptosis in a broader context. The balance between oxidative stress and antioxidant defenses is crucial in determining cell fate and the role of boron should be understood within this framework. Furthermore, the potential side effects and optimal dosage of boron in clinical settings need to be further investigated to ensure its safe and effective use in cancer therapy.

Antioxidant activity of boric acid and boron-containing compounds

Oxidative stress has been linked to a variety of diseases, including chronic obstructive pulmonary disease, atherosclerosis, cancer and Alzheimer's disease (AD),

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revealing the numerous routes via which oxidants cause cellular damage [171–174]. However, the degree to which oxidative stress participates in the pathogenesis of diseases is quite diverse, therefore the effectiveness of strengthening antioxidant defense may be limited with regard to some diseases [171–173]. Oxidative stress is characterized by a disrupted balance between reactive oxygen species (ROS) generation and antioxidant effectiveness [172]. A compromised antioxidant system could contribute as well to disease pathogenesis [173, 175].

Boron can act as an indirect proton donor, influencing the structure and function of cell membranes [176]. Therefore, it has been proposed that cyclic adenosine monophosphates (cAMP), whose concentrations rise as a result of boron's effects, may disrupt the metabolism of mitochondrial oxidative phosphorylation and inhibits the activities of hydrolytic enzymes [177]. The antioxidative properties of boron compounds such as BA, borax, colemanite, and ulexite in neuronal cells are thought to be linked to their roles in mitochondrial dynamics [178].

The investigations looked into BA as a potential novel antioxidant medication. BA therapy reduced lipid peroxidation, decreased the expression of proinflammatory cytokines, and enhanced the function of the antioxidant defense system in the cell line. Also, the findings revealed that BA effectively lowered formaldehyde-induced oxidative stress and inflammation by blocking lipid peroxidation and preventing the depletion of antioxidant enzymes [179]. Gündoğdu et al (2024) established in their studies that BA protects gastric mucosa from ethanol-induced injury by modifying the oxidative and inflammatory responses [106]. By analyzing prenatal alcohol-induced oxidative stress in the cerebral cortex of newborn rat pups and assessing the protective and advantageous effects of BA supplementation in rats with fetal alcohol syndrome (FAS), Sogut et al (2015) examined the impact of BA administration on FAS. The findings showed that alcohol may harm rat pups' cerebral cortex and that BA may be useful in antioxidant defenses against oxidative stress brought on by prenatal alcohol exposure [180]. Moreover, different compounds have been shown to enhance antioxidant enzyme activities at low supplementation levels without causing oxidative stress in blood cells [181]. Ince et al (2014) found that 20 mg/kg BA treatment alleviated focal gliosis and neuronal degeneration in the brains of rats treated with CP [182]. Another study reported that 100 mg/kg BA partially reduced the effects of arsenic-induced oxidative stress [183]. In conclusion, these findings suggest that BA at various doses may reduce the effects of oxidative stress in tissues by supporting antioxidant enzymes. Additionally, it has been proposed that BA could protect nerve morphology by influencing cellular antioxidant mechanisms and safeguarding axons from the destructive effects of oxidative stress [184].

Antimicrobial activities of boric acid and boron-containing compounds

Recent years included an enormous rise in the literature of boron and its anti-microbial traits. The emergence of FDA-approved boron-based pharmaceuticals has altered the view of boron as an injurious agent [79]. Boron and metals are being researched as potential treatments for microbial resistance and as competitors to antibiotics [185]. The current scientific literature substantially supports boron's antibacterial, antifungal and antiviral traits. However, future research might focus on gauging their mechanisms of action to try to clarify the possible uses in medical use.

Antibacterial activity of boric acid and boron-containing compounds

Modern pharmacology places a strong emphasis on the creation of antimicrobial agents that are both safe and effective [186]. Based on existing experiments obtained from scientific literature, it has been discovered that boron and its compounds possess antibacterial properties. Sayin and Ucan (2016) showed that BA has demonstrated antibacterial and anti-biofilm effects on specific bacterial strains. This capability suggests that new methods could be developed for the use of various functional microorganism tests in medical and industrial applications [187]. Celebi et al (2024) studied the antibacterial activity of nine boron derivatives against biofilm-forming pathogenic bacteria [188]. They found that sodium metaborate tetrahydrate is effective against all pathogens and identified methicillin-resistant *Staphylococcus aureus* (MRSA) as the bacterium with

the strongest biofilm-forming ability. Additionally, boron derivatives were determined to be non-toxic to fibroblast cells (L929) at low concentrations (1 μg/L) and exhibited significant inhibitory activity against biofilm-forming pathogens during short treatment periods [188]. According to the study by Uzun-Yaylacı et al (2021), 3.09 and 1.54 mg/mL concentrations of BA have been shown to be effective against aquatic pathogens such as *Aeromonas veronii* [189]. Also, the blend of ascorbic acid and curcumin-BA has been proved to be useful in treating *Salmonella enteritidis* infections [190]. In the study by Brittingham and Wilson (2014) demonstrating the antimicrobial effect of BA on *Trichomonas vaginalis*, BA concentrations above 0.1% had a important effect on the growth and viability of *T. vaginalis*. Concentrations of 0.4% or greater completely inhibited the growth of parasites. Additionally, BA was shown to exhibit strong antimicrobial activity against *T. vaginalis* across a broad physiological pH range [191]. Moreover, boron-based compounds such as boronic acids have demonstrated strong antibacterial activity as β-lactamase inhibitors against Gram-negative bacteria. Boronic acids and borinic esters have shown versatile potential in antibacterial strategies by targeting penicillin-binding proteins, quorum sensing mechanisms, and methyltransferases. Optimization of these compounds could enable the development of new and effective treatments against resistant bacteria [192]. However, further molecular studies are needed to better understand the effects and mechanisms of these compounds.

Antifungal activity of boric acid and boron-containing compounds

The natural human microbiota of the skin, oral, GI, and genitourinary tracts includes *Candida* species. Only a small number of the 200 or so species in the genus Candida are opportunistic infections in humans. Candida-caused invasive infections are particularly significant in severely ill patients admitted to intensive care units [193]. The most prevalent species linked to invasive fungal infections is *Candida albicans* [194]. Currently, boron components are known to have antifungal effects [195]. BA has been used as a topical antifungal drug for vaginal infections for many years [196]. In the study conducted by De Seta et al (2009), *C. albicans* strains were inhibited at intravaginally achievable concentrations. They reported that BA exhibited fungistatic properties, as indicated by a decrease in CO_2 production. BA works by decreasing oxidative metabolism, which lowers cellular ergosterol production and interferes with hyphae transformation by preventing apical development through cytoskeletal disruption [197]. Likewise, BA breaks down cytoskeletal processes, such as actin rearrangement, in Candida hyphal production, leading to aberrant hyphal development, according to Pointer and colleagues [198]. Larsen et al (2018) aimed to investigate whether organoboron compounds provide antifungal activity similar to BA and whether they possess other beneficial properties in addition to their antifungal effects. To this end, they examined the sensitivity of Candida species to BA and organoboron compounds. The study found that *C. glabrata* was inhibited by both BA and organoboron compounds, and that organoboron compounds have potential as topical therapeutics [199]. Furthermore, the *in vitro* antifungal effects of pure boron were investigated against yeasts and molds isolated from patients with superficial mycosis caused by Candida, Trichophyton, and *Aspergillus fumigatus*. The study's findings demonstrated that boron prevented the growth of molds and yeasts. At very low quantities, boron showed antifungal action when diluted in distilled water with an alkaline pH. As a result, it is proposed that boron might be a substitute for conventional antifungals in the treatment of superficial mycosis [200].

Antiviral activity of boric acid and boron-containing compounds

In late December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared, causing a pandemic of acute respiratory disease known as "coronavirus disease 2019" (COVID-19), which poses a hazard to human health [201, 202]. The COVID-19 pandemic poses an obstacle in determining efficacious drug therapy approaches for both prevention and treatment [201, 202]. According to recent data, COVID-19 infection may be effectively managed by therapeutic drugs with antiviral, anti-inflammatory, and immunomodulatory qualities [202, 203]. Thus, boron citrate and oleoylethanolamide (OEA)

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have been investigated in COVID-19 patients by Akbari et al (2022). The study's results showed that O_2 saturation and respiratory rate were markedly enhanced by boron citrate supplementation, either by itself or in conjunction with OEA. Furthermore, the boron citrate and combination groups showed notable increases in the number of white blood cells and lymphocytes [204]. Moreover, curcumin has a unique chemical structure that makes it a potential chelating agent [205]. Its esters interact with BA to generate rosocyanine, a complex that is frequently used to measure the quantity of boron in different organic and inorganic matrices [206]. Curcumin decreased the inhibition activity of human immunodeficiency virus (HIV)-1 and HIV-2 proteases, whereas rosocyanine boosted the inhibition activity of HIV-1 and HIV-2 proteases by more than ten times [207]. These substances are thought to have potential applications as medications in the future to enhance blood circulation throughout the body and prevent pandemic viral attacks like SARS-CoV-2. In conclusion, a number of boron-based chemicals could be made to prevent COVID-19 viral illness and curcumin's capacity to create boron complexes [208]. Additionally, *in silico* studies have demonstrated that BCCs may exhibit antiviral effects against viral conditions through docking analysis [209, 210].

Antiprotozoal and antiparasitic activities of boric acid and boron-containing compounds

Parasitic diseases are among the world's most severe and widespread infections, affecting millions of morbidities and deaths each year. Presently, however, climate and vector ecological changes, a major increase in international travel, armed conflicts, human and animal migration have impacted the transmission of various parasitic diseases in developed countries [211]. Using a variety of dosage schedules, four case reports demonstrated *Trichomonas vaginalis* clearance with BA. According to *in vitro* research, BA has pH-independent anti-*T. vaginalis* action. Intravaginal BA may offer a well-tolerated alternative anti-infective treatment that reduces the population's need of systemic antibiotics if it is shown to be safe and effective [212]. BA was used to amidate benzenesulfonamides in Ugwu et al (2018) investigation on the synthesis of novel carboxamide derivatives comprising substituted benzenesulfonamides against human African trypanosomiasis parasite infection. The work showed that novel carboxamides with exceptional yields were generated by amidation of benzenesulfonamides and p-aminobenzoic acid mediated by BA [213]. Particularly in the underdeveloped countries, infectious disorders brought on by protozoan parasites constitute a substantial unmet medical need [214–216]. *Trypanosoma brucei*, *Plasmodium falciparum*, and *T. cruzi* are among the significant protozoan diseases that have been found to be susceptible to the intriguing activity of a class of boron-containing chemicals known as benzoxaboroles in recent years [217]. Lindenthal et al (2005) demonstrated that the boronate analog MLN-273 inhibits *P. falciparum*'s intraerythrocytic development and *P. berghei*'s exoerythrocytic development [218]. ZL3B and bortezomib, two boronates, were shown by Reynold et al (2007) to be strong inhibitors of the intraerythrocytic cycle in *P. falciparum* strains that are both drug-sensitive and resistant [219].

Antiobesity activity of boric acid and boron-containing compounds

The WHO considers the rapid rises in obesity prevalence across all age categories, particularly since the 1970s, to constitute a global obesity epidemic. Today, obesity affects roughly 650 million adults, and 340 million children and adolescents aged 5 to 19 years [220, 221]. Given the absence of a definitive treatment for obesity, these studies explored the potential of this substance as a novel therapeutic option aimed at alleviating symptoms and modifying disease progression. It was reported in literature that BA inhibited adipogenesis in common cellular models. In the model by Doğan et al (2017), BA and sodium pentaborate pentahydrate ($Na_2B_4O_7 \cdot 10H_2O$) therapy suppressed the expression of adipogenesis-related proteins and genes, as well as decreased mitotic clonal expansion through cell cycle gene regulation [222]. Aysan et al (2011) have investigated the influence of oral BA administration on body weight and have discovered that a very low dose (0.2 mg/kg) oral BA administration results in substantial body weight reduction in mice [223]. Also, Farrin et al (2022)

have conducted a meta-analysis to analyze the effect of BA on body weight. According to findings, BA administration orally resulted in a considerable decrease in body weight [224].

Antidiabetic activity of boric acid and boron-containing compounds

Diabetes mellitus is a severe global public health issue. It affects 463 million people globally, and by 2045 this figure may rise to 700 million [225]. Diabetes mellitus is a metabolic disorder defined by high or low levels of fasting blood glucose, caused by the partial or complete lack of insulin hormone and the equivalent damage to carbohydrate, lipid, and protein metabolism [226]. Based on the lack of definitive treatment for diabetic diseases, the studies have investigated the potential of this substance as a novel therapeutic option for alleviating symptoms and slowing disease progression. Previous study by Cakir et al (2018) found that increased serum lipid peroxidation levels with diabetes significantly decreased, and although not statistically significant, serum TAC levels came towards those of the control group; additionally, insignificant increases in high-density lipoprotein cholesterol (HDL-C) levels were observed in experimental diabetic administration BA on rats with two groups [227]. In addition, lipase activities, low-density lipoprotein (LDL) and blood glucose serum cholesterol have reduced significantly in the diabetes BA with one group [227]. According to the findings of this recent study by Cakir (2024), the increase in total cholesterol triglyceride, glucose, LDL-cholesterol levels and ALT, AST activities in streptozotocin-induced groups were decreased with BA administration [228]. While HDL-C levels dramatically reduced in the streptozotocin group, they approached control group levels following BA treatment. Although peptide levels increased statistically significantly following BA administration, they did not approach the control group values. Cakir's research suggests that BA might be an appealing therapeutic element [228].

Effects of boric acid and boron-containing compounds on the immune system

Immunity is essential for preserving health because it shields the body from infection by both endogenous and foreign pathogens [229]. There have been some documented effects of boron compounds on the immune system [230–233]. Recent studies on the impact of BA on the differentiation of lymphocyte clusters in mice and rats are among these [229, 234]. Routray and Ali (2016) demonstrated that T and B-cell populations in mice significantly increased following oral borax delivery, as seen by an increase in CD4 and CD19 [234]. Also, the lipopolysaccharide (LPS)-primed macrophages' production of TNF-α, interleukin 6 (IL-6), IL-1β, nitric oxide (NO), and inducible nitric oxide synthase (iNOS) was induced by borax [234]. Jin et al (2017) showed that adding rats' drinking water with 20 and 40 mg/L of boron raised their serum immunoglobulin G levels, hemoglobin concentrations, leukocyte, erythrocyte, lymphocyte, and monocyte counts, induced an increase in splenic $CD3^+$ T cells [229]. This improved both general and specific immune responses. Furthermore, it raised the amount of $CD4^+$ T cells in the spleen and the number of $CD4^+/CD8^+$ T cells. This led to the spleen producing and secreting more IL-2, interferon-gamma (IFN-γ), and IL-4, which improved cellular immune activities [229].

Antiatherosclerotic activity of boric acid and boron-containing compounds

Plaque buildup inside arteries causes atherosclerosis, a cardiovascular condition that can result in fatalities, heart attacks, and strokes [235]. Development and progression of atherosclerotic coronary arteries result in coronary heart disease. Depending on degree of artery damage, angina or heart attack occurs [236, 237]. Among the main treatments for atherosclerosis are statins, which lower serum levels of LDL and cholesterol and stop the production of foam cells [238]. Also, antioxidant-based treatments have been explored because inflammation and lipoprotein oxidation play important roles in the development of atherosclerosis [238]. Boron may be a viable alternative for maintaining a healthy cardiovascular system because it plays a role in the control of signaling pathways related to inflammation, oxidative stress, or lipid metabolism [239]. Some studies have shown that BCCs may provide protection against atherosclerosis through their antioxidant effect by reducing ROS and SOD activities [240–242]. Moreover, a study by Asadi et al (2023), in which animal models with atherosclerosis were given 4 mg/kg BA, showed that BA could prevent atherosclerosis over time by

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preventing lipid buildup and cholesterol absorption from tissues [235].

Effects of boric acid and boron-containing compounds on wound healing

One of the biggest and fastest-growing issues in the world today is wounds. The incidence of chronic wounds has increased, particularly as a result of the fast aging of the population and the rise in the prevalence of chronic illnesses [243]. Chronic wounds are those that exhibit abnormalities during the healing process [244]. Chronic wounds are particularly vulnerable to bacterial colonization and biofilm formation because of the lack of the epithelial barrier and the high pH of the surrounding environment. This can lead to severe oxidative stress, an inflammatory storm, and impaired angiogenesis. Wound healing is further hampered by these pathological alterations [245]. The process of wound healing is dynamic and involves the cooperative action of several cells, growth factors, proteins, and cytokines [246]. It is well known that BA, a dynamic and advantageous trace element, contributes to the healing of wounds [1, 247]. Because of their effects on the extracellular matrix, BA shows a notable improvement in the wound healing process [248]. According to a study by Roy et al (2010), which used hydrogel wound dressing containing BA, hydrogels were very flexible and had potent antibacterial qualities. So, the use of boron as a wound dressing care material was advised [249]. Demirci et al (2016) showed exceptional antibacterial properties of BA and NaB against bacteria, yeast, and fungi in addition to considerably increasing the proliferation, migration, essential growth factors, and gene expression levels of dermal cells. Furthermore, they demonstrated that the gel formulation containing NaB improved wound healing rates and histopathological scores in diabetic animal models created in rats [250]. Moreover, the most recent findings show that mixing NaB with pluronic block polymers increases cell migration, SOD activity, gene expression linked to essential wound contraction and healing of human primary fibroblast cells, and collagen deposition [251]. *In vitro* study's findings showed that erbium borate nanoparticles are a suitable substance for scarless wound healing [252]. Kurtoğlu and Karataş (2009) demonstrated that wounds that occurred in the lower limbs as a result of diabetes caused weak blood circulation, and that wound dressings having boron content were useful in wound healing when systemic antibiotic treatment was ineffective [253]. Chupakhin et al (2017) also found that hydrogels containing silicone and boron enhanced wound healing, regeneration, and antibacterial activity in an *in vitro* investigation [254]. In conclusion, despite the fact that the precise mechanism of boron in wound healing remains unclear, some boron compounds like BA show a variety of therapeutic actions during the healing process. These include encouraging angiogenesis, inducing TNF-α secretion by macrophages, increasing neutrophil migration and activation, boosting fibroblast proliferation and activation, encouraging keratinocyte migration and proliferation, and exhibiting antibacterial properties [255, 256].

Protective roles of boric acid and boron-containing compounds

Cardioprotective effect

About 30% of deaths worldwide are caused by cardiovascular diseases (CD), which include a variety of conditions affecting the heart and blood vessels as well as the negative consequences they are linked to [257]. It has long been recognized that a lack of boron in soils causes a decrease in BCCs in food, which has been linked to an increased risk of arthritis, an inflammatory condition that is also linked to cardiovascular health [258, 259]. Potential advantages for the cardiovascular system are suggested by the beneficial impact of natural organic BCCs on lipid levels. The two main risk factors for CD are oxidative stress and chronic low-grade inflammation. Through nicotinamide adenine dinucleotide (NAD+) and/or cyclic adenosine diphosphate ribose binding, BCCs have been demonstrated in numerous studies to regulate oxidative stress and inflammatory responses [90, 260]. Additionally, a study by Karimkhani et al (2021) concluded that in their study's statistical analysis that BA had preventive effects on cellular damage in MI; electrocardiography and light microscope results backing up the findings [261]. Furthermore, almost all types of cardiac disorders, especially heart failure (HF), are related to myocardial fibrosis (MF). Trans-differentiation of fibroblasts, the appearance of myofibroblasts, and the early activation of pro-fibrotic signaling pathways

prior to unfavorable ventricular remodeling are the earliest characteristics of MF. In a rat model of MI-induced HF, the study examining the effects of borax, a sodium salt of boron, supplementation on cardiac function, MF, apoptosis, and regeneration revealed that borax treatment significantly improved systolic and diastolic functions when compared to the control [262]. Borax treatment showed a significant decrease in MF and apoptosis in injured hearts, underscoring borax's preventive role in ischemic hearts [262]. Additionally, compared to the saline group, the MI borax-treated rats showed ten times as many nuclei positively stained for the cell cycle marker Ki67 in thin myocardial slices. Crucially, it may promote the entry of cardiomyocytes into the cell cycle and maybe promote the regeneration of damaged cardiac muscle [262].

Hepatoprotective effect

The liver is essential for the body's metabolism and toxin removal. Liver ailments are among the most urgent global health concerns [263, 264]. Herbal and natural chemicals play a major role in the curing of liver disorders [265]. By regulating insulin release and aiding in the metabolism of energy substrates, boron salts may play a crucial role in regulating lipid and energy metabolism [266]. It has been stated by Abdik et al (2021) that giving mice NaB might lower the weight of their liver and white adipose tissue while also suppressing adipogenic genes [267]. The study by Şahin et al (2023) also revealed that NaB and BA supplementation boosted peroxisome proliferator-activated receptor gamma (PPARγ) expression while decreased sterol regulatory element-binding protein 1c (SREBP-1c), liver X receptor alpha (LxR-α), and FAS expression in the liver of rats, which is in line with earlier research showing the effects of BA and NaB on genes associated to lipid metabolism [267–269]. Furthermore, it was shown that by blocking LxR-α and the LxR-α/SREBP-1c/FAS cascade, BA and NaB could control lipogenesis in the rat liver [268]. Moreover, liver damage occurs with an overdose of acetaminophen (APAP) [270]. Accordingly, Çelik and Aydın (2022) investigated the efficacy of 4-hydroxyphenylboronic acid (4-OHFBA), a boronic acid derivative, in APAP-induced liver damage [271]. It was demonstrated that increased AST and ALT levels, markers of cell death and liver cell damage, decreased with 4-OHFBA treatment, while cell viability in the HepG2 cell line increased. These findings suggest that 4-OHFBA may be effective in APAP-induced cell death and liver damage and boron compounds' antioxidant and anti-inflammatory properties have considerable promise in liver injury treatment [271].

Neuroprotective effect

Pharmacological study indicates that boron compounds have neuroprotective properties [35]. Several studies in recent years have shown that BA has a strong neuroprotective effect in a range of *in vitro* and *in vivo* models of neuronal injury. According to Turkez et al (2022), boron compounds, particularly BA, borax, and ulexite, can be given to people at specific dosages to help avoid hematological and neurological diseases [178]. Many neurological illnesses are characterized by oxidative stress [272]. Anti-inflammatory and antioxidant abilities of boron compounds can lessen neuroinflammation and protect nerves [273].

Effects of boric acid and boron-containing compounds on diseases

Antiparkinson's disease activity

Parkinson's disease (PD) affects an estimated 8.5 million individuals worldwide, as reported by the WHO [274]. PD is a neurodegenerative condition defined by dopaminergic cell death in the substantia nigra compacta nigra pars, and the disease produces uncontrollable movements known as motor symptoms such as bradykinesia, tremors, dystonia and rigidity [275, 276]. Given the absence of a definitive treatment for PD, the studies explored the potential of this substance as a novel therapeutic option aimed at alleviating symptoms and modifying disease progression.

BA's pharmacological, behavioral, and biochemical effects on rats with experimental PD produced by rotenone were examined in a study by Ozdemir et al (2022), BA showed dose-related improvement, notably in the brain tissue and there was noticed significant rise in tyrosine hydroxylase immunoreactivity [276]. In a study investigating the ameliorative effects of hexagonal boron nitride nanoparticles (hBNs) against 1-methyl-4-phenylpyridinium (MPP+) toxicity in an experimental PD model, the results showed that hBNs increased

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cell viability and that TAS and TOS analyses revealed an increase in antioxidant capacity and a reduction in oxidant levels after hBN application [277]. Furthermore, the administration of hBNs considerably inhibited MPP+-induced apoptosis. Therefore, the results suggest that hBNs have great potential against MPP^+ toxicity and may serve as a novel neuroprotective agent in PD treatment [277]. In the study by Yavuz et al (2023), the effects of BA and quercetin (QCT) on oxidative stress markers and behavioral tests were investigated. These results of the study indicate that the combined application of BA and QCT positively affects the oxidant-antioxidant balance by preventing the pathogenesis of PD [278].

Antialzheimer's disease activity

AD, which accounts for 60-70% of dementia cases, is a neurological ailment that normally begins slowly and worsens with time [279]. Approximately 60% of the world's 55 million dementia patients live in low- and middle-income countries [280]. Aggregation of amyloid beta (Aβ) peptides is a key component in the etiopathogenesis of AD [281]. Pharmacological therapies are currently being researched that will block or decrease the nerve deterioration that causes AD, and the FDA approved drugs only temporarily ease symptoms by boosting neurotransmitter levels in the brain [282]. In AD, the most common kind of dementia, oxidative stress plays a significant pathophysiological role [283]. BA has an important function in protecting the brain by lowering lipid peroxidation and increasing antioxidant defense [280]. Özdemir et al (2023) showed that in rats with streptozotocin-induced dementia, BA administration improved learning and memory abilities by lowering oxidative stress [283]. The stereological and histopathological findings of Çolak et al (2011) demonstrated that BA, as a proteasome inhibitor, can lessen the negative impacts of aluminum chloride on the cerebral cortex [284]. Moreover, in both *in vitro* and *in vivo* models of AD, some studies have discovered that certain BCC treatments, such as 2-aminoethylborinic acid or borolatonin, significantly reduced inflammation in a pathogenic association with Aβ buildup [35]. Also, Lu et al (2018) produced a number of new BCCs that act as multi-target-directed ligands against AD. According to the study, these substances have a strong capacity to prevent self-induced Aβ aggregation and may have antioxidant properties [285].

Effects on osteoporosis

Osteoporosis affects an estimated 200 million people worldwide, with one in every three women over the age of 50 and one in every five males over the age of 50 suffering from osteoporosis-related fractures. Osteoporosis is a metabolic bone disorder characterized by microarchitectural deterioration and low bone mass of the bone tissue, resulting in lesser bone strength and an increased risk of low-energy fractures or fragility [286–290]. Boron contributes favorably to calcium metabolism, which is a highly significant factor in preventing osteoporosis and bone loss [88]. Xu et al (2023) in their *in vitro* studies demonstrated that BA therapy for 5 days suppressed osteoclastic bone resorption and osteoclast formation in a dose-dependent manner [291]. BA reduced the expression of osteoclast markers such as cathepsin K, nuclear factor of activated T cells 1, c-Fos and tartrate-resistant acid phosphatase. BA also inhibited receptor activator of NF-κB ligand-induced activation of the protein kinase R-like endoplasmic reticulum kinase-eukaryotic initiation factor 2α pathway, as shown by immunoblotting studies. According to their in-vivo findings, BA significantly decreased LPS-induced bone loss [291]. Moreover, Toker et al (2016) also shown in their study that BA may reduce alveolar bone loss in a rat model with periodontitis and osteoporosis [292].

Effects on ischemia/reperfusion

A pathological state known as ischemia and reperfusion (I/R) is defined by an initial restriction of an organ's blood supply, followed by a subsequent restoration of perfusion and simultaneous reoxygenation [293]. Organ ischemia can have serious repercussions such as cerebral infarction and MI, leading to irreparable tissue damage [294, 295]. Tissue reperfusion helps to prevent further ischemia; but, in some instances, it may worsen the injury via a process known as I/R injury, which may take place in many organs and result in incapacity, severe diseases and even death [293, 296, 297]. A protective agent against I/R injury is BA. BA has promising results according to Güler et al (2021) in the treatment of experimental I/R injury of the cholestatic liver because of its antioxidant

properties [298]. Also, Çolak et al (2022) explored the role of BA in ovarian tissue damage induced by I/R, demonstrated that BA has a protective effect on ovarian tissue against I/R damage in the rat model [299].

Effects on epilepsy

About 50 million individuals worldwide suffer from epilepsy, a chronic, recurring, and progressive neurological condition [297]. The presence of paroxysmal, self-limited convulsive or non-convulsive seizures characterizes epilepsies, which are persistent neurological diseases [300–302]. All forms of epilepsies include recurrent and spontaneous seizures, which are defined by synchronized high-frequency firings of brain neuronal populations [303, 304]. Being a complex condition with a wide variety of clinical characteristics, epilepsy cannot be sufficiently explained by a single pathogenic process. It is known that *in vivo* studies have been conducted on epilepsy, and in these studies, the effects of BA and BCCs have also been investigated [35]. To ascertain the impact of BA on epileptiform activity, Karademir and Arslan (2019) administered four distinct dosages of BA half an hour after injecting penicillin. Proconvulsant action was demonstrated by BA treatment without altering the spike amplitude. The antiepileptic medication gabapentin decreased the frequency of spike activities and when combined, BA prevented gabapentin's anticonvulsant effects [305].

The effects of boric acid and boron-containing compounds on cell viability

BA has been shown to significantly affect the viability and osteogenic differentiation of adipose-derived mesenchymal stem cells, with no observed toxic effects on these cells [306]. A study by Lu et al (2020) investigated the effects of BA at seven different concentrations on cultured rat Sertoli cells [307]. The results showed that concentrations of 0.5 mmol/L and below increased cell viability and resulted in the lowest rates of necrosis and apoptosis. However, as the concentration increased, toxic effects on the cells were observed, leading to decreased cell viability and increased necrosis and apoptosis [307]. In a study where different concentrations of borax pentahydrate (BPH) were applied to human umbilical vein endothelial cells (HUVEC), BPH was reported to have a selective effect on HUVEC viability [308]. Ozansoy et al (2020) investigated the effects of two BCCs, sodium borate decahydrate and BA, against Aβ toxicity. The results showed that both compounds enhanced the survival of SH-SY5Y cells in an *in vitro* Aβ model. These boron compounds increased the expression of SIRT1, a protein with a protective function against cellular stress [34]. Additionally, in a study by Turkez et al (2022), various boron compounds (colemanite, ulexite, BA, and borax) were tested and found not to cause any cytotoxic damage in human blood cells or rat primary cortical neurons [178].

Safety and toxicity

It is of great importance to understand the safety profiles of BCCs, which have a wide range of uses from industrial applications to agriculture, from pharmaceuticals to materials science. Studies on the effects on human health reveal that the toxicological properties of boron and its derivatives vary depending on the level and duration of exposure [90]. The mechanisms primarily responsible for the toxicity of the boron compounds involve interference in cell membrane permeability and enzyme systems. BA and its derivatives have been found to react in a cis-diols of biomolecules. A typical interaction might interfere with essential biomolecule function, for instance, ribose containing molecules NAD+ and RNA [309]. Most acute inorganic boron toxicities have relatively low to moderate. For the first one, LD50 oral was set for 2660 mg/kg body weight for BA. It can also show GI irritation symptoms on acute contact-mostly characterized by vomiting and diarrhea [310]. In long-term exposure, the effects of boron compounds on the reproductive system come to the fore. The studies conducted in cases of occupational and environmental exposure showed that effects such as a decrease in the quality and number of sperms in the male reproductive system and ovulation disorders in females can be observed [311]. The studies performed regarding the metabolic effects of boron compounds revealed very important findings in postmenopausal women. Studies on the daily intake of boron through diet and its effects on health also reveal positive effects, primarily relating to bone metabolism. In a controlled study, Hunt et al (1994) showed that low intake of boron at 0.25 mg per day increased urinary

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calcium excretion and impaired magnesium metabolism in subjects compared to high boron intake of 3.25 mg per day [312]. Results from experiments underscore the need for adequate boron intake for mineral metabolism [310–312]. Randomized controlled trials demonstrated that boron supplementation is likely to positively impact bone mineral density [258]. Mechanistic studies show that the involvement of boron relates to steroid hormone metabolism and vitamin D homeostasis [312]. In conclusion, toxic manifestations of boron and its compounds are related to the level and duration of exposure. Available scientific data on the industrial and agricultural use of boron compounds indicate that such applications have an acceptable safety profile, provided that proper precautions are taken, and the limits of exposure are not exceeded.

CONCLUSION

The prevalence of boron in natural goods and its overall safety as a mineral have garnered considerable interest from health science researchers. The findings of the extensive review indicate that BA and some BCCs exhibit significant effects, including neuroprotection, cardioprotection, hepatoprotection, gastroprotection, antidiabetic properties, and antimicrobial, antibacterial, antifungal, antiviral, antiprotozoal, antiparasitic, anti-obesity, antioxidant, anti-inflammatory, anti-atherosclerotic, anticancer, anti-apoptotic, ferroptosis-related, and immune-related effects.

As a result, synthetic BCCs have been created in recent years, accompanied by a significant rise in both preclinical and clinical research. At now, 5 BCCs drugs (tavaborole, vaborbactam, bortezomib, crisaborole and ixazomib) have been approved by the FDA for diverse clinical applications. It is also understood that more than 10 boron-based compounds (alabostat, TOL-463, sodium borocaptate, voromycin and others) are being investigated in different clinical trial phases. In addition, it is seen that clinical studies are continuing for combinations of various drugs with BCCs for use in new indications.

In addition, it is observed that boron and boron-containing compounds are widely used as supplements. It is known that boron and boron-containing compounds are used in various pharmaceutical forms; capsules, tablets, chewing gums, liquid and powder (or antifungal and antibacterial applications) forms, fortified foods and beverages, boron-enriched mineral waters and functional foods containing boron compounds.

The consensus is that most toxic research involving boron focus on BA. BA is readily absorbed by the gastrointestinal tract. Boron is primarily believed to be excreted via urine; however, it has been noted that it is also eliminated through the gastrointestinal tract following the application of hazardous quantities of boron transdermally. BA has demonstrated deadly effects in numerous instances following cutaneous and oral administration in preclinical trials. Preclinical study results indicated an absence of genotoxicity and carcinogenicity. Chronic investigations have demonstrated that BA is non-carcinogenic.

The chemical characteristics of boron augment its medicinal potential. Boron is extensively employed in research as a reversible covalent moiety in peptides for protease inhibition, owing to its reversible electrophilicity. Moreover, boronic acids and boron esters, which demonstrate stability and binding at physiological pH, work as bioisosteres for ionized functional groups like carboxylates, esters, and phosphates, thus enhancing pharmacokinetic qualities, biological activity, or structural attributes.

Current research indicates that boronic acids may enhance the delivery of drugs and macromolecules by incorporating into lipid bilayers for liposomal transport or by reversibly binding to proteins. These findings underscore boron's potential for innovative therapeutic applications and the enhancement of its clinical value. BA and several BCCs demonstrate considerable potential for the development of novel therapeutic strategies for human diseases.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS' CONTRIBUTION

Oruc Yunusoglu — concept development, conducting the study, preparation and editing the text, approval of the final version; Oruc Yunusoglu, Irem Kalfa, Mustafa Enes Demirel, Muhammed Ali Binzet, Uygar Zarif Sevinc, Idris Turel and Akif Hakan Kurt — concept development, conducting the study, preparation and editing the text, approval of the final version Oruc Yunusoglu, Irem Kalfa — conducting the study; Oruc Yunusoglu, Irem Kalfa, Idris Turel and Akif Hakan Kurt — conducting the study, resource support of the study; Oruc Yunusoglu, İrem Kalfa — conducting the study; Oruc Yunusoglu, Irem Kalfa and Muhammed Ali Binzet — conducting the study. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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AUTHORS

Oruc Yunusoglu — Assistant Professor of the Department of Medical Pharmacology in Faculty of Medicine, Bolu Abant Izzet Baysal University. ORCID ID: 0000-0003-1075-9574. E-mail: orucfarm@gmail.com

Irem Kalfa — Master's degree student of Medical Pharmacology Department in Faculty of Medicine, Bolu Abant Izzet Baysal University. ORCID ID: 0009-0002-5658-1011. E-mail: iremkalfa24@gmail.com

Mustafa Enes Demirel — Doctor of Sciences (Medicine), Faculty Member of the Department of Emergency in Faculty of Medicine, Bolu Abant Izzet Baysal University. ORCID ID: 0000-0001-5187-5737. E-mail: mustafaenesdemirel@ibu.edu.tr

Muhammed Ali Binzet — Candidate of Sciences (Medicine), Doctor in Faculty of Medicine, Bolu Abant İzzet Baysal University. ORCID ID: 0009-0006-4368-6745. E-mail: binzetmuhammedali@gmail.com

Uygar Zarif Sevinc — Master's degree student of the Department of Medical Pharmacology in Faculty of Medicine, Bolu Abant Izzet Baysal University. ORCID ID: 0009-0006-4354-8182. E-mail: uygar.zarif@outlook.com

Idris Turel — Doctor of Sciences (Medicine), Professor, Head of the Department of Medical Pharmacology in Faculty of Medicine, Bolu Abant Izzet Baysal University. ORCID ID: 0000-0001-6614-4347. E-mail: idristurel@ibu.edu.tr

Akif Hakan Kurt — Doctor of Sciences (Medicine), Professor of the Department of Medical Pharmacology in Faculty of Medicine, Bolu Abant Izzet Baysal University. ORCID ID: 0000-0003-2940-3172. E-mail: hakankurt@ibu.edu.tr

Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ
(PHARMACY & PHARMACOLOGY)

EDITORIAL

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CORRIGENDUM: Microbiological landscape and parameters of antibiotic resistance of pathogens in patients of neonatal intensive care units [Pharmacy & Pharmacology. 2024;12(6):378-393. DOI: 10.19163/2307-9266-2024-12-6-378-393]

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We hereby inform readers that in the final version of the article changes were made in Russian and English.

In the published article "Microbiological landscape and parameters of antibiotic resistance of pathogens in patients of neonatal intensive care units", there was an error. In the authors' affiliations did not include all institutions and positions held: Butranova O.I. – Research Fellow of IPCE RAS, Moscow, Russia; Gorbacheva A.A. – Research Engineer IPCE RAS, Moscow, Russia; Zyryanov S.K. – Chief Research Fellow of IPCE RAS, Moscow, Russia.

Correct version:

O.I. Butranova[1, 2], A.A. Gorbacheva[1, 2, 3], S.K. Zyryanov[1, 2, 4], O.G. Ni[3]

[1] Peoples' Friendship University (RUDN University),
6 Miklukho-Maklaya Str., Moscow, Russia, 117198
[2]Institute of Physical Chemistry and Electrochemistry of Russian Academy of Sciences,
bldg. 4, 31, Russia, Leninsky Prospekt, Moscow, 119071
[3] Kommunarka Center,
8/3 Sosenskiy Stan Str., Moscow, Russia, 108814
[4] City Clinical Hospital No. 24,
10 Pistsovaya Str., Moscow, Russia, 127015

О.И. Бутранова[1, 2], А.А. Горбачева[1, 2, 3], С.К. Зырянов[1, 2, 4], О.Г. Ни[3]

[1] Федеральное государственное автономное образовательное учреждение высшего образования
«Российский университет дружбы народов имени Патриса Лумумбы»,
Россия, 117198, г. Москва, ул. Миклухо-Маклая, д. 6
[2] Федеральное государственное бюджетное учреждение науки
Институт физической химии и электрохимии им. А.Н. Фрумкина Российской академии наук,
Россия, 119071, г. Москва, Ленинский проспект, д. 31, корп. 4
[3] Государственное бюджетное учреждение здравоохранения города Москвы
«Московский многопрофильный клинический центр «Коммунарка»
Департамента здравоохранения города Москвы»,
Россия, 108814, г. Москва, ул. Сосенский Стан, д. 8/3
[4] Государственное бюджетное учреждение города Москвы «Городская клиническая больница № 24
Департамента здравоохранения города Москвы»,
Россия, 127015, г. Москва, ул. Писцовая, д. 10

AUTHORS

Olga I. Butranova – Candidate of Sciences (Medicine), Assistant Professor of the Department of General and Clinical Pharmacology of the Medical Institute, Peoples' Friendship University (RUDN University); Research Fellow of IPCE RAS. ORCID ID: 0000-0001-7729-2169. E-mail: butranova-oi@rudn.ru

Anastasiia A. Gorbacheva – Assistant Lecturer of the Department of General and Clinical Pharmacology of the Medical Institute, Peoples' Friendship University (RUDN University); Research Engineer IPCE RAS; Clinical Pharmacologist of Kommunarka Center (Moscow, Russia). ORCID ID: 0009-0003-9721-6931. E-mail: gorbacheva_aa@pfur.ru

Sergey K. Zyryanov – Doctor of Sciences (Medicine), Professor, Head of the Department of General and Clinical Pharmacology of the Peoples' Friendship University (RUDN University); Chief Research Fellow of IPCE RAS; Deputy Chief Physician of the City Clinical Hospital No. 24 (Moscow, Russia). ORCID ID: 0000-0002-6348-6867. E-mail: zyryanov_sk@rudn.university

Oksana G. Ni – Head of the Department of Clinical Pharmacology of the Kommunarka Center (Moscow, Russia). ORCID ID: 0000-0003-0994-0579. E-mail: ni.oksana@gmail.com

Due to a technical error on part and without any malicious intent, it was stated in the "Funding" section that "This study did not have financial support from third-party organizations."

The authors regret that the following statement was missed out due to oversight in the Funding section in the version of this article initially published: "The research was carried out at the expense of the Russian Science Foundation No. 23-73-30004, https://rscf.ru/project/23-73-30004 /"

Correct version:

FUNDING

The research was carried out at the expense of the Russian Science Foundation No. 23-73-30004, https://rscf.ru/project/23-73-30004/

The error does not change the essence of the data presented in the article, does not violate their perception by readers or interpretation.

The authors would like to apologize for any inconvenience caused. The authors declare no conflict of interest.

The original article has been updated in online-version: https://www.pharmpharm.ru/jour/article/view/1667

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EDITORIAL

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CORRIGENDUM: Problems and Solutions of Pharmaceutical Packaging in Bulk [Pharmacy & Pharmacology. 2025;13(2):128-138. DOI: 10.19163/2307-9266-2025-13-2-128-138]

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We hereby inform readers that in the final version of the article changes were made in Russian.

In the published article “Problems and Solutions of Pharmaceutical Packaging in Bulk”, the authors found an error: accidentally, due to a technical error on our part and without any malicious intent, source No. 17 was incorrectly indicated in the “References” section of the Russian-language version of the article:

17. Фисенко В.С., Соломатина Т.В., Фаррахов А.З., Юрочкин Д.С., Мамедов Д.Д., Мальченкова С.С., Голяк Н.С. Современное состояние экстемпорального изготовления лекарственных средств в Федеративной Республике Германия // Вестник фармации. – 2022. – № 3(97). – С. 44–56. https://doi.org/10.52540/2074-9457.2022.3.44

The authors regret that, due to oversight, the indicated source of literature was incorrectly cited in the originally published version of this article.

Correct version:

17. Мальченкова С.С., Голяк Н.С. Современное состояние экстемпорального изготовления лекарственных средств в Федеративной Республике Германия // Вестник фармации. – 2022. – № 3(97). – С. 44–56. https://doi.org/10.52540/2074-9457.2022.3.44

The error occurred due to the fault of the entire team of authors, but does not change the essence of the data presented in the article, does not violate their perception by readers or interpretation.

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EDITORIAL

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
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CORRIGENDUM: Regulation in the sphere of circulation of extemporaneously compounded medicines under modern conditions of Russia

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We hereby inform readers that
in the final version of the article changes were made in Russian and English.

In the published article " Regulation in the sphere of circulation of extemporaneously compounded medicines under modern conditions of Russia", the authors found an error: accidentally, due to a technical error on part and without any malicious intent, ehe regulatory document was incorrectly specified in table 1 (p.330):

Resolution of the Government of the Russian Federation No. 546 "On Approval of the Regulations on Licensing of Pharmaceutical Activities" dated March 31, 2022.

The authors regret that, due to an oversight, the cited regulatory document was incorrectly numbered (No. 546) in the originally published version of this article.

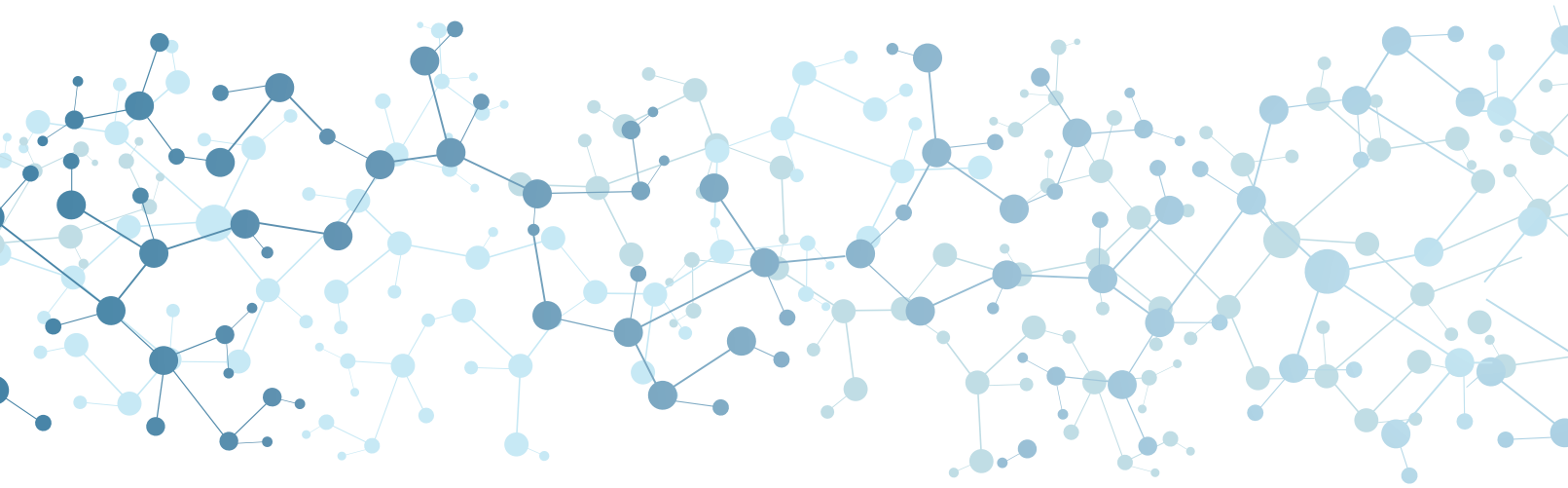
Correct version:

Resolution of the Government of the Russian Federation No. 547 "On Approval of the Regulations on Licensing of Pharmaceutical Activities" dated March 31, 2022.

The error occurred due to the fault of the entire team of authors, but does not change the essence of the data presented in the article, does not violate their perception by readers or interpretation.

The authors would like to apologize for any inconvenience. The authors declare no conflict of interest.

The original article has been updated in online-version: https://www.pharmpharm.ru/jour/article/view/1664

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