

REVIEW ARTICLE

Evaluation of topical remedies in the treatment of acne available in the Republic of Moldova

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Date of receipt of the manuscript: 14.04.2022

Date of acceptance for publication: 30.05.2022

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Titlu scurt: Topical remedies in the treatment of acne

What is not yet known on the issue addressed in the submitted manuscript

Pharmaceutical manufacture is in a continuously developing and improving state, including the formulations customized for dermato-cosmetics use in order to identify the most effective topical treatment for acne, which would improve the symptoms and diminished the negative impact on the quality of life of patients.

The research hypothesis

The systematization of data from the literature and evaluation of local pharmaceutical market on the topical treatment of acne would allow the unification of national and international therapeutic patterns and formulation of practical recommendations.

The novelty added by manuscript to the already published scientific literature

Current status and trends of the contemporary and effective pharmacotherapeutic approach in the treatment of acne and its availability for patients. Collation between topical industrial pharmaceutical forms and magistral individual compounded drugs, prescribed by dermatologists from the Republic of Moldova based on the data from Production department of the Vasile Procopisin University Pharmaceutical Center.

Summary

Introduction. A lot of research and studies are currently being carried out in the field of elaboration and optimization of topical pharmaceutical forms used in the treatment of various types of acne. *Acne vulgaris* is a disease with a complex etiopathogenesis with potential negative psychosocial effects on the quality of life of patients, and its prevention is based on the successful management of risk factors. There are currently many topical and systemic treatment options available, so the choice of therapy depends on the form and severity of the condition. The advantage of topical pharmaceutical forms is the ability to target early stages of acne lesions.

Material and methods. Statistical, systemic, informational and sociological analysis were used as methods of analysis. Documentation with the State Drug Nomenclature and Classification, evaluation of topical prescription for acne treatment, dispensed in the Vasile Procopisin University Pharmaceutical Center (UPhC), the study of active pharmaceutical ingredients (API) and technological characteristics of topical pharmaceutical forms.

Results. Topical treatment for acne should be based on its type and severity. The basic therapy for the treatment of mild acne refers to external applications, due to their action to prevent lesions. Treatment should be maintained over time to prevent recurrence. For domestic patients are accessible drugs with keratolytic, bacteriostatic and anti-inflammatory properties for topical treatments as benzoyl peroxide, salicylic acid, sulfur, azelaic acid, zinc oxide and antibiotic. The analysis of the use of anti-acne medications, in treating mild to moderate acne, by the age group, identified that for adolescents treatment is being focused on combating the causative agent of sebum production using salicylic acid in 32.5% cases and with age increase, the aim is to suppress inflammatory processes requiring retinoids, and in case of absence, can be substituted by benzoyl peroxide.

Conclusions. The therapeutic approach in clinical practice must be done individually, considering the severity and shape of acne lesions.

Keywords: acne, industrial, magistral, topical pharmaceutical forms.

Introduction

Currently, guidelines for the treatment of acne, as well as safety, tolerability and patient preferences are needed to determine the appropriate treatment steps. The literature may support evidence-based physician recommendations based on these factors. Thus, the bibliographic references,

are focused on the efficacy and tolerability of the combined topical therapies used in the treatment of acne. Proceeding from the multifactorial pathogenesis of acne and the obstacles to adherence to treatment, scientists opt for optimization of topical anti-acne pharmaceutical forms which shall lead to greater confidence in the future of patients [1].

Acne vulgaris is a chronic dermatological condition that affects about 80% of adolescents globally, of which 20% have a mild and severe form. The age of onset is between 10 and 17 years for females and between 14 and 19 years for males, but it can also occur at an older age [2, 3]. Acne is an inflammatory condition of the pilosebaceous unit of the

skin, which occurs through excessive production of sebum, which leads to the formation of comedones, by blocking the pilosebaceous unit, by hyperkeratinization hair, blocking the elimination of sebum, with the formation of blackheads, and by added bacterial infections [4]. Anaerobic *Propionibacterium acnes* develops in acne lesions, maintaining inflammation and forming whitehead lesions characteristic of acne: papules, pustules, nodules and cysts, as shown in figure 1. Acne is often associated with seborrhea, so it affects especially the areas where the sebaceous glands are more abundant: face, head, neck, upper part (chest and arms) [5].

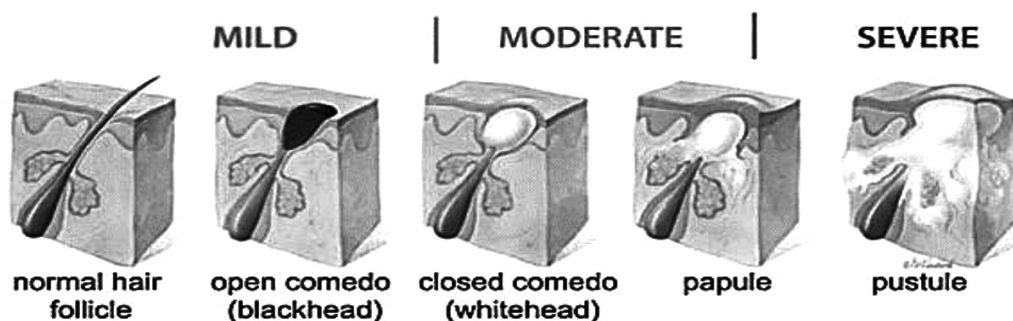


Fig. 1. The stages of acne [6].

Topical therapy in acne vulgaris includes multiple options: retinoids, antibiotics, substances with antibacterial, keratolytic, antimicrobial action (salicylic acid, sulfur, chloramphenicol, etc.). The choice of topical therapy is influenced by the patient's age, the location of the lesions, their extent and severity, as well as the patient's preference [6, 7].

According to international specialized literature, the most commonly used medications for the treatment of various forms of acne are *topical retinoids* (vitamin A derivatives), known for 4 generations to bind the specific retinoid receptors at the keratinocyte level, they reduce keratinization and follicular adhesion, leading to inhibition of comedogenesis and increased skin penetration for other topical treatments [8]. In international dermatological practice, retinoids are recommended for topical use due to their anti-comedogenic and anti-inflammatory effects as initiation or maintenance therapy and also for relapse prevention [9-11]. The combination of a topical retinoid with an antimicrobial agent is recommended as a first-line treatment for most patients, as it targets the multiple pathological factors that underlie the appearance of inflammatory and non-inflammatory acne lesions [12]. Retinoids stimulate the turnover of epithelial cells, with the release of the cutaneous pilosebaceous unit, and have anti-inflammatory properties by inhibiting the chemotaxis of neutrophils and monocytes [3]. Their impact varies with vehicle formation, skin type, frequency and mode of application, use of moisturizers, and environmental factors such as sun exposure or temperature [13, 14].

Current research, in accordance with published guidelines and protocols, considering the effectiveness, safety and tolerability of anti-acne treatment, as well as patient allegations can help the physician to achieve an effective evidence-based effect on all factors that cause acne.

The aim of this study is to get an overview of the current and future direction of topical pharmacotherapy for acne and evaluate industrial drugs and magistral formulations available in the Republic of Moldova, also to identify the most prescribed API (active pharmaceutical ingredients) by domestic dermatologists.

Material and methods

In order to achieve the purpose of the paper, the materials used were in the form of scientific publications, national and international guides on the methods of treatment of various forms of acne. As methods of analysis were applied statistical, systemic, informational, and sociological analysis. Analytical evaluation of State Drug Nomenclature and Classification of the administrative authority Agency for Medicines and Medical Devices by pharmaceutical active ingredients and manufacturing countries, also evaluation of the magistral prescriptions of the *Vasile Procopisin* UPhC (University Pharmaceutical Center) regarding topical pharmaceutical forms used in the treatment of acne by age groups (11-16 y.o., 17-21 y.o., 21-28 y.o., 29 y.o. and more), by pharmaceutical form (ointments, pastes, creams, liniments) and by pharmaceutical active ingredients.

Results and discussions

There is currently a wide variety of anti-acne treatment options available in the R. of Moldova, offering integrative therapeutic approaches so that they are tailored to the patient's needs. The choice of treatment depends on the etiopathogenic cause of the acne, the personal or family history, the treatment used previously and the response obtained to these therapies, in association with a thorough clinical examination of the patient. Due to the fact that acne is a condition that can lead to psychosocial impairment of patients, it is important to start treatment as early as possible [15, 16]. The goals of anti-acne therapy is to reduce the number and severity of existing lesions, to prevent the formation of new lesions and the formation of permanent scars, leading to disfigurement. Thus, for anti-acne therapy, specialists from the R. of Moldova approach a complex treatment, in which topical therapy is associated with systemic therapy. For instance, in the Republic of Moldova at the moment is registered the 1st generation retinoid - *isotretinoin* - for oral administration in the form of capsules.

Topical therapy is the first intention in mild and moderate cases of acne, and the combination of several topical preparations for various aspects of acne pathogenesis may be useful. Most often dermatologists from different curative-prophylactic institutions opt for industrial pharmaceutical forms and mainly, in the form of ointment, cream, gel, suspension and local applications. In patients with sensitive skin prone to acne, doctors often prescribe such pharmaceutical forms as ointments-emulsions, liquid creams, hydrogels, which have permeable properties (moisturizing), but do not make skin oily, are easily washable, and are more effective from a biopharmaceutical point of view [17]. The penetration of topical drugs into and through the skin can be achieved in two ways: (1) through the pores - the walls of the hair follicles (transfollicular) and less through the sweat glands; (2) transepidermal - passing through the epidermis.

Thus, the skin absorbs the following categories of substances: substances soluble in skin lipoids (nonpolar organic solvents); substances soluble in both oil and water; fat-soluble volatile substances, due to a wide variety of ointment bases [18]. The factors that influence the penetration of topically administered drugs and implicitly the bioavailability and the action of the pharmaceutical form are the factors related to the structure and conditions of the skin, characteristics of the active and auxiliary substances, the composition of the applied topical formula, a special role being played by the vehicle - the excipient or the ointment base.

Nowadays, there is a wide assortment of dermatoproducts with singular or multicomponent medicines. Pharmaceutical industry has entered a new era, as there is a growing interest in increasing the standards of quality of dosage forms, through the implementation of more structured development and manufacturing technologies [19]. For topical formulation, as a semi-solid dosage form, that has suitable consistency for the treatment of skin diseases caused by bacteria, a key challenge relay to the properties of the active

substance in association with excipient bases [20] and the objective in development includes physical-chemical studies of API proprieties and excipients and their compatibility, release rate, stability, *in vitro* and *in vivo* drug permeability studies, etc. Industrial topical anti-acne dosage forms are available in various pharmaceutical forms, majority with conventional, unmodified API release, such as: gels, ointments, creams, lotions, etc. On domestic pharmaceutical market are present dermato-products containing benzoyl peroxide, azelaic acid, sulfur and other substances, as displayed in table 1.

Table 1. Topical industrial preparations used in the treatment of acne available in the Republic of Moldova

International common name of the API	Pharmaceutical form, concentration
Benzoyl peroxide	Cream, 5%
Azelaic acid	Cream 20%, gel 15%
Erythromycin	Gel 25 mg/g
Clindamycin	Gel 10 mg/g
Sulfur	Paste, 10%
Zinc oxide	Paste, 10%, ointment, 100 mg/g
Salicylic acid	Ointment 30 mg/g

Evaluation of registered anti-acne industrial pharmaceutical forms available in our country revealed that the drugs are from different chemical groups starting with:

- benzoyl peroxide is used as an alternative to topical retinoids, associated with antibiotics in the treatment of acne. Benzoyl peroxide has comedolytic effects by increasing the renewal rate of epithelial cells and by favoring the opening of pores blocked by excess sebum and cell debris [21, 22]. Benzoyl peroxide side effects occur especially if high doses are used at the beginning of treatment. These side effects are excessive dry skin, flaking, erythema, sensitization and contact dermatitis [23, 24], if the allergic event is severe, the treatment is interrupted; benzoyl peroxide produces photosensitization; like retinoids, it is contraindicated in pregnancy [25]. Benzoyl peroxide used alone can relieve inflammatory acne, with antibacterial, anti-inflammatory and keratolytic action [26]. The decomposition of benzoyl peroxide releases oxygen as a by-product. The oxygen suppresses the growth of anaerobic bacteria *P. acnes* [27]. By hindering bacterial colonization in sebaceous ducts, oxygen markedly reduces bacterial count (even over 95% during 2 weeks).

- azelaic acid, as a dicarboxylic acid, has antibacterial, comedolytic and anti-inflammatory properties. It is considered an effective topical treatment for adult patients with acne and for maintenance therapy. A potential adverse effect of azelaic acid is the appearance of hypopigmented lesions, so it can be used in the treatment of post-inflammatory hyperpigmentation [28, 29].

- topical antibiotics, erythromycin and clindamycin are most commonly used in the treatment of acne. Erythromycin is used both in reducing inflammatory lesions and

in reducing non-inflammatory lesions. After its use for 6 to 12 weeks, a reduction in lesions was observed in 42% to 74% for inflammatory lesions and between 25% and 74% for non-inflammatory lesions [23]. Combined with zinc, erythromycin is much more effective in reducing pustules and papules [30]. Clindamycin is a lincosamide derivative, with antimicrobial action is effective in fighting gram-positive and gram-negative microorganisms, has the following effects – destroys bacteria, disinfects, regenerates cells, cleanses, dries, whitens [31].

- the sulfur commonly prescribed by dermatologists in pharmaceutical suspensions is known to be a very good agent in eliminating acne, it helps to absorb chemicals from the skin that are the main cause of acne. Sulfur acne treatment is done by drying excess fat on the skin and controlling sebum [32]. It makes the surface of the skin to peel off. This exfoliation helps to produce new cells, which leads to firmer and smoother skin.

- zinc oxide has the ability to act like a mild astringent. It will keep *P. acnes* from causing infections and acts as a natural skin-drying agent. Thus, zinc oxide on acne-prone

skin treatment may help clear acne-causing bacteria and reduce oil production [33].

- salicylic acid is a topical medication and is found in a variety of anti-acne, one-component liquid and semi-solid forms and in combined formulations of alpha and beta hydroxy acids [14].

Doctors recommend starting the treatment with low doses of benzoyl peroxide (2.5%) as they have a lower irritant effect compared to higher concentration preparations [34]. Because of the risk of developing bacterial resistance when erythromycin and clindamycin are used as monotherapy, if prescribed, they should be combined with benzoyl peroxide [25].

After evaluation of State Drug Nomenclature of medicines [35] that are registered in the R. of Moldova, we had established that the major share of topical drugs used in acne belongs to domestic manufacturer of pharmaceuticals and that salicylic acid is the most utilized component in anti-acne products registered from different countries. Local pharmaceutical manufacture *Farmaprim LTD* produce drugs containing chloramphenicol, salicylic acid, sulfur and benzoyl peroxide, as shown in figure 2.

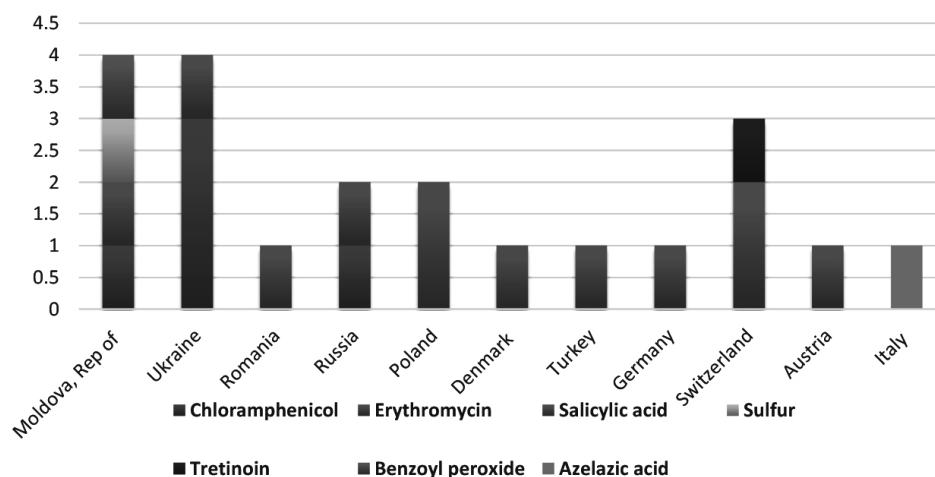


Fig. 2. Anti-acne drugs registered in the Republic of Moldova, by the countries of manufacture, in units.

An important direction in anti-acne treatment is emphasized by preparation by compounding pharmaceutical formulations according to medical prescriptions. Dermatologists from various medical institutions from our country prescribe in the treatment of acne magistral or extemporaneous prescriptions for drug preparation in pharmacies as topical formulations containing: salicylic acid, sulfur, chloramphenicol, and others. The evidence-based medication of individual medication maintains the trend for compounding. Pharmacies are still individually responsible for assessing the quality, stability, and effectiveness of every compounded preparation they dispense.

Compounding is an extemporaneous process and a compounded topical anti-acne product, formulated based on individual unique prescription by pharmacists, is more susceptible to physicochemical modifications than manufactured drug

products that are made usually by a single drug. Thus, a proper combination of more than one active and inactive ingredients, in consideration of the quality, stability, and effectiveness of compounded preparations, rely on pharmacy technicians. Following the analysis of the prescription from *Vasile Procopisin* UPhC it was determined that the pharmaceutical forms for topical use (ointments, pastes, gels, ointments-emulsions, ointments-suspensions, creams, etc.) represent 4-6% of the total preparations prescribed by doctors and prepared by pharmacists. Among topical forms that are prepared and released, pastes occupy the largest share – 25.6% (figure 3), followed by ointments with water-oil base – 21.4%, that are considered to have advantages as dermato-cosmetics because after been applied on skin, evaporation occurs and increases the release concentration of the drug that was previously dissolved in water, thus enhancing the API effect and absorption.

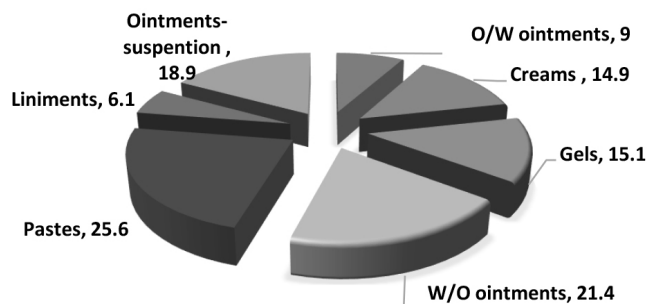


Fig. 3. The share of topical anti-acne pharmaceutical forms in Vasile Procopisin UPhC, %.

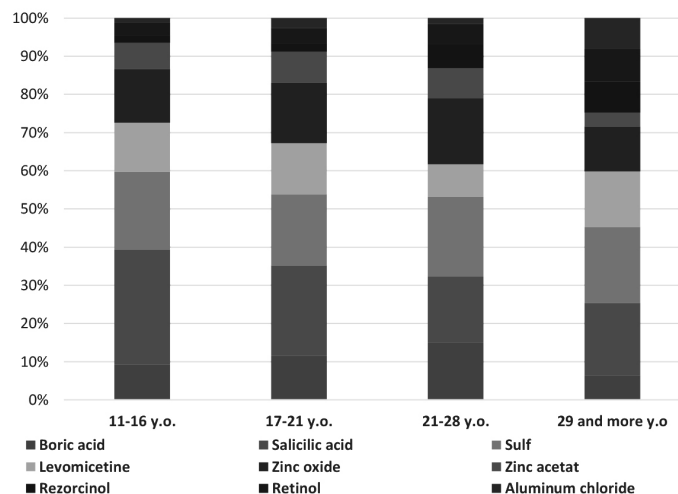


Fig. 4. Evaluation of compounded magistral-prescribed active substances by age group, %.

Evaluation of prescribed anti-acne API by dermatologists from the R. of Moldova was carried out. Following analysis of the prescriptions, based on the age of the patients, it was found that the most common API indicated in the age groups of 11-16 and 17-21 years (figure 4) is salicylic acid; sulfur is prescribed for both the juvenile segment and the adult group over 29 years of age, including the most common retinol and resorcinol.

Salicylic acid ointment is prescribed by doctors in a concentration of 1% for magistral formulations. It has a comedolytic effect, but with a lower efficiency than topical retinoids. Sulfur, commonly prescribed by dermatologists in pharmaceutical ointments-suspension, is known to be a very effective agent in eliminating acne because it helps to absorb chemicals from the skin that are the main cause of acne. Sulfur acts on acne on account of keratolytic properties and helps to quickly get rid of dead skin cells that block pores, which causes acne. It also clears comedones and prevents them from forming again. This exfoliation helps to produce new cells, which leads to firmer and smoother skin. The analysis revealed that the treatment of acne in adolescents focuses on combating the causative agent of sebum production, and with increasing age, the aim is to suppress inflammatory processes.

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Conclusions

Acne vulgaris is considered a minor clinical problem but has a significant psychosocial impact on the patient's quality of life, leading to psychological stress or depression. Specialists pay attention not only to the physical manifestations of acne, but also to the emotional burdens resulting from the condition.

Currently on the pharmaceutical market there is a wide range of topical industrial forms, favored by salicylic acid. In the production department of *Vasile Procopisin* UPhC there is a large assortment of anti-acne remedies, with different therapeutically groups of medicinal substances that are prescribed in magistral prescription by dermatologists.

Pharmaceutical compounding of topical anti-acne remedies is opportune for continuous research in pharmaceutical optimization regarding dermato-products perusing an efficient and safety anti-acne pharmacotherapy.

Declaration of conflict of interest

The author declares the absence of any conflict of interest in the elaboration of this article.

Authors' contribution

All authors participated equally in the elaboration and writing of the paper. All authors read and approved the final version of the manuscript.

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