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MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
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QUALIFICATION WORK

on the topic: «**OPTIMIZING THE USE OF TOPICAL RETINOIDS IN MOROCCAN PATIENTS WITH ACNE**»

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ANNOTATION

Ikram Agountaf. Optimizing the use of topical retinoids in Moroccan patients with acne. – The manuscript. – National University of Pharmacy of Ministry of Healthcare of Ukraine, Kharkiv, 2023.

In the qualification work practical recommendations to improve medication adherence in type acne patients are developed.

The conditions of rational use of retinoids, alternative ways of increase of efficiency and safety of therapy of patients and ways of increase of quality of life of patients with acne are offered.

Qualification work is presented on 42 pages of typewritten text, consists of summary, introduction, 3 chapters, conclusions, references. The work is illustrated with 11 tables, 4 figures. The list of references contains 50 resources.

Key words: adherence, acne, topical retinoids, healthcare providers, efficacy and safety of therapy, quality of life

АНОТАЦІЯ

Ікрам Агунтаф. Оптимізація застосування топічних ретиноїдів у марокканських пацієнтів з акне. – На правах рукопису. – Національний фармацевтичний університет МОЗ України, Харків, 2023.

У кваліфікаційній роботі розроблено практичні рекомендації щодо покращення прихильності до лікування хворих на акне.

Запропоновано умови раціонального використання топічних ретиноїдів, альтернативні шляхи підвищення ефективності та безпеки терапії хворих та шляхи підвищення якості життя хворих на акне.

Кваліфікаційна робота викладена на 42 сторінках машинописного тексту, складається з резюме, вступу, 3 розділів, висновків, списку літератури. Робота проілюстрована 11 таблицями, 4 рисунками. Список літератури містить 50 найменувань.

Ключові слова: прихильність, акне, топічні ретиноїди, медичні працівники, ефективність та безпека терапії, якість життя

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INTRODUCTION

Relevance of the topic. Acne has been a known skin condition since ancient times, but it was not until the 19th century that it was identified as a distinct medical issue. The term «acne» is derived from the Greek word «acme», which means «peak» or «point». It is a prevalent skin disorder, with its incidence peaking during adolescence and early adulthood, affecting approximately 85% of individuals between the ages of 12 and 24. Although commonly associated with teenagers, acne can affect individuals of any age, though it becomes less frequent as one grows older. Nevertheless, more than a quarter of women and 12% of men in their 40s report experiencing acne. Acne is one of the most common reasons adult women between the ages 20 to 40 come to the dermatology clinic is for acne. Clinical trial data revealed that approximately 50% of women in their 20s, 33% of women in their 30s, and 25% of women in their 40s suffer from acne. The good news is there are many treatment options available to help [15, 16, 26, 43].

Acne vulgaris is a persistent skin condition that affects the pilosebaceous unit and results from blockages in the hair follicles. The blockages are caused by four abnormal processes, namely, increased sebum production due to androgen activity, accumulation of protein keratin causing the formation of comedones, colonization of the hair follicle by Cutibacterium acnes (C. acnes) bacteria, and the local release of pro-inflammatory chemicals in the skin. The development of acne begins with the formation of a plug called a microcomedone, which results mainly from the excessive growth, reproduction, and accumulation of skin cells within the hair follicle. In normal skin, dead skin cells exit the pore of the hair follicle and reach the skin's surface. However, in acne-prone skin, the increased production of sebum causes the dead skin cells to stick together, leading to the accumulation of debris and blockage of the hair follicle, forming a microcomedone. The presence of C. acnes biofilm within the hair follicle exacerbates this process. If the microcomedone is close to the skin's surface, the melanin pigment is exposed to air, oxidizes, and turns dark, resulting in a blackhead or open comedo. On the other hand,

if the microcomedone is deep within the hair follicle, it leads to the formation of a closed comedo or whitehead [28].

Treatments for acne are available, including lifestyle changes, medications, and medical procedures. Reducing the intake of simple carbohydrates, such as sugar, may help reduce the occurrence of acne. Topical treatments such as azelaic acid, benzoyl peroxide, and salicylic acid are commonly used to treat acne on the affected skin. Antibiotics and retinoids are also available in formulations that can be applied topically or taken orally. However, prolonged use of antibiotics may result in antibiotic resistance. Certain types of birth control pills can help prevent acne in women. Isotretinoin pills are typically prescribed for severe acne due to the potential for significant side effects. Some medical professionals recommend early and aggressive treatment of acne to minimize its long-term impact on individuals [19].

Topical retinoids are considered a key component of acne treatment as they can eliminate mature comedones, reduce the formation of microcomedones, and have anti-inflammatory effects. In the United States, first-generation retinoid tretinoin (all-trans retinoic acid) and third-generation polyaromatics, such as adapalene and tazarotene, have been approved by the FDA for the treatment of acne. In Canada and Europe, topical tretinoin, isotretinoin (13-cis retinoic acid), and adapalene are accredited for the same purpose. Topical retinoids have a positive safety profile that differs from the toxicity associated with their systemic counterparts. During the initial treatment phase, local side effects such as erythema, dryness, itching, and stinging frequently occur. The effects vary depending on the formulation, skin type, frequency and method of application, use of moisturizers, and environmental factors such as sun exposure or temperature. Due to their broad anti-acne activity and safety profile, topical retinoids are a suitable first-line treatment for most types of non-inflammatory and inflammatory acne. They can also be used as long-term medications to maintain remission after discontinuing initial combination therapy, without the risk of inducing bacterial resistance [12, 29].

Topical retinoids are the drugs of choice for the treatment and maintenance therapy of patients with mild-to-moderate acne vulgaris. They can be used alone or

in combination with benzoyl peroxide and either topical or oral antibiotics, depending on the severity of the acne. Oral antibiotics are effective for inflammatory acne that does not respond to topical therapy. However, neither topical nor oral antibiotics should be used as the sole treatment. Women with acne may benefit from oral contraceptives and/or spironolactone. Severe, extensive, nodular acne vulgaris is best treated with oral isotretinoin. However, it is also commonly used in moderate cases where there is evidence of scarring, significant acne-related emotional distress, or where other treatment options have failed [17, 30].

The aim of the study. The aim of the thesis is optimizing the use of topical retinoids in Moroccan patients with acne.

The objectives of the study. Objectives of the work are the following:

1. To investigate the Epidemiology and pharmacoepidemiology of acne.
2. To investigate approaches to acne treatment in modern dermatology practice.
3. To study the opinion and beliefs of dermatologists concerning efficiency criteria and essential factors of treatment of acne.
4. To study the opinion and beliefs of patients with acne concerning efficiency criteria and essential factors of the use of topical retinoids.
5. To develop practical recommendations for healthcare professionals (doctors and pharmacists) to increase the efficiency of treatment of acne.

Object of research: pharmacotherapy of acne.

Subject of research: medication adherence in patients with acne, effectiveness and safety of treatment.

Research methods. Questionnaire for pharmacy visitors with acne; statistical (using the program «Statistica 6.0», Student's t-test).

Structure and scope of qualification work. Qualification work is presented on the 42 pages of typewritten text, consists of summary, introduction, 3 chapters, conclusions, references. The work is illustrated with 14 tables, 4 figures. The list of literature contains 50 references.

CHAPTER 1
MODERN PRESENTATION ABOUT ACNE, APPROACHES TO TREATMENT (LITERATURE REVIEW)

1.1 Epidemiology and pharmacoepidemiology of acne

Acne, also known as acne vulgaris, is a prevalent condition that can lead to various negative outcomes and expenses. Some of these consequences include physical discomfort, scarring, emotional and psychological distress, impact on employment, and the possibility of mental health issues such as depression and suicidal thoughts. Identifying individuals who are susceptible to these consequences can aid in decreasing the overall negative effects associated with acne [11, 25, 27].

From the mid to late 20th century, the majority of epidemiological studies on acne were performed in the United states of America and the UK. The largest of these was a population-based study of over 20 000 Americans whose acne was evaluated by dermatologists or residents. Similar smaller studies were performed in the UK. with approximately 1/10 the sample size. Studies from that era demonstrated that the age of peak incidence for acne was the late teens, with progressive reduction in prevalence with increasing age. Male patients were more frequently affected, particularly with more severe forms of acne. Seminal studies on adolescent maturation and acne included longitudinal studies in American schoolchildren. These showed that the prevalence and severity of acne increased with pubertal maturation and that comedonal acne predominated in preteens, with increasing inflammatory acne developing during the teen years [6].

Over the past decade, the typical age range for individuals with acne has risen from 20.5 years to 26.5 years old. Research has revealed that acne may increase the likelihood of experiencing depression. Severe depression is twice as common in people with acne, with 11% being affected compared to those without acne. Additionally, a study found that 96% of individuals with acne have reported feeling depressed due to their condition. This has caused 46% to develop self-esteem is-

sues related to their complexion, and 31% to withdraw from social activities and remain at home [44].

Till 2010, acne affected approximately 650 million people, or about 9.4% of the population. It affects nearly 90% of people in Western societies during their teenage years, but can occur before adolescence and may persist into adulthood. While acne that first develops between the ages of 21 and 25 is uncommon, it affects 54% of women and 40% of men older than 25 years of age and has a lifetime prevalence of 85%. About 20% of those affected have moderate or severe cases. It is slightly more common in females than males (9.8% versus 9.0%). In those over 40 years old, 1% of males and 5% of females still have problems [31, 45].

Acne rates seem to be lower in rural societies. Although some studies have found that it affects people of all ethnicities, there are reports that acne may not occur in non-Westernized populations such as those in Papua New Guinea and Paraguay. In the United States, acne affects 40-50 million people (16%), while in Australia, it affects approximately 3-5 million (23%). Severe acne is more common in people of Caucasian or Amerindian descent than in those of African descent. This information is from the source cited in the article.

In 2019, acne vulgaris was responsible for 4.96 million (95% CI 2.98-7.85) DALYs, of which 3.52 million (95% CI 2.11-5.64) occurred in the 15-49 year age group. In the 10-24 year age group, acne was the 27th most common cause of increasing DALYs in 1990, accounting for 1.1% of DALYs, and rising to the 19th position in 2019, accounting for 1.6% of DALYs. Acne can have a significant impact on quality of life and mood, leading to an increased risk of anxiety, depression, and suicidal thoughts among those affected.

Types of acne [20, 36]:

Non-inflammatory acne, which consists of blackheads and whiteheads, typically does not cause inflammation or swelling and is often treated successfully with over-the-counter (OTC) products. Salicylic acid is a common OTC treatment for acne, but it is most effective for non-inflammatory acne as it exfoliates the skin and removes dead skin cells that can lead to blackheads and whiteheads.

Blackheads, or open comedones, occur when a pore becomes clogged by a combination of sebum and dead skin cells, but the top of the pore remains open despite the blockage, resulting in the characteristic black color on the surface.

Whiteheads, or closed comedones, can also form when a pore is clogged by sebum and dead skin cells, but in this case, the top of the pore closes up, resulting in a small bump on the skin's surface. Whiteheads are more challenging to treat since the pores are already closed, but products containing salicylic acid can be helpful. For comedonal acne, topical retinoids provide the best results, with adapalene (Differin) being an OTC option. If OTC treatments are not effective, stronger topical retinoids are available with a prescription from a dermatologist.

Inflammatory acne, characterized by red and swollen pimples, can be caused by a combination of sebum, dead skin cells, and bacteria clogging up the pores. Infection deep beneath the skin can also lead to painful acne spots that are difficult to eliminate. Benzoyl-peroxide-containing products can help to reduce swelling and bacteria within the skin, as well as removing excess sebum. Oral or topical antibiotics may also be prescribed by a doctor to treat inflammatory acne, along with topical retinoids for papules and pustules [46].

Papules are hard, clogged pores that are tender to touch, they occur when the walls surrounding the pores break down from severe inflammation. The skin around these pores is usually pink.

Pustules can also form when the walls around the pores break down. Unlike papules, pustules are filled with pus. These bumps come out from the skin and are usually red in color. They often have yellow or white heads on top.

Nodules: unlike pustules and papules, nodules are deeper underneath the skin. when clogged, swollen pores endure further irritation and grow larger. Because nodules are so deep within the skin, they can’t be typically treated at home.

Prescription medication is necessary to help clear these up. The doctor or dermatologist will likely prescribe the oral medication isotretinoin.

Cysts: can develop when pores are clogged by a combination of bacteria, sebum, and dead skin cells. The clogs occur deep within the skin and are further be-

low the surface than nodules. These large red or white bumps are often painful to the touch, and their formation usually results from a severe infection. This type of acne is also the most likely to scar [47].

To summarize, these findings provide an updated assessment of the increasing public health burden posed by acne around the world. Acne vulgaris, and the scars it leaves, can lead to significant social and academic challenges that may persist into adulthood. In fact, during the Great Depression, it was noted that young men with acne had difficulty securing employment. Prior to the 1930s, acne was often dismissed as a minor issue affecting middle-class girls, as it was not a fatal disease like smallpox or tuberculosis. Additionally, it was considered a feminine issue since boys were less likely to seek medical attention for it. During World War II, soldiers stationed in tropical climates developed such severe and widespread tropical acne that many were deemed medically unfit for duty.

Severity of acne [34]:

Grade 1 (mild): Mostly whiteheads and blackheads, with a few papules and pustules.

Grade 2 (moderate or pustular acne): Multiple papules and pustules, mostly on the face.

Grade 3 (moderately severe or nodulocystic acne): Numerous papules and pustules, along with occasionally inflamed nodules. Your back and chest may also be affected.

Grade 4 (severe nodulocystic acne): Numerous large, painful and inflamed pustules and nodules.

Topical treatments offer the benefit of targeting the affected area directly, resulting in lower systemic absorption and increased exposure of the pilosebaceous units to the treatment. Nevertheless, a significant drawback of anti-acne topical products is skin irritation. These products are accessible in different formulations, such as creams, gels, lotions, solutions, and washes, for topical application [21, 22].

For mild acne, topical retinoids or a range of other treatments such as azelaic acid, salicylic acid, and benzoyl peroxide are commonly used. In cases of mild to

moderate inflammatory acne, topical anti-inflammatory agents and antibiotics can be effective. Topical anti-acne medications target various pathophysiological factors, and some of the commonly used treatments will be discussed below.

Retinoids Topical retinoids can be used as monotherapy for inflammatory acne, as a maintenance treatment or in combination with more severe forms of acne. They are effective in controlling the formation of microcomedones, reducing the development of lesions and existing comedones, decreasing sebum production, and normalizing epithelial desquamation. By targeting microcomedones, they suppress comedone formation and may also exhibit anti-inflammatory properties.

As suggests Gollnick and Krautheim:

1). the use of topical retinoids is vital for maintenance treatment;

2). retinoids can repair the scarring and hyperpigmentation of the skin;

3). this class of drugs should be first choice of treatment for most of the acne types;

4). when combined with topical antimicrobials it is more effective in inflammatory acne. A common side effect during the first few weeks of topical retinoid treatment is a flare up of acne. This should, however, be clear as the patient continues with the treatment. Only some of the most common topical retinoids (i.e., tretinoin, adapalene and tazarotene) used in acne treatment will be discussed”

Tretinoin, a type of vitamin A, is a common comedolytic agent used in acne treatment to regulate epithelial desquamation, which helps prevent pilosebaceous unit blockage. It also exhibits anti-inflammatory properties and has been a topical treatment for acne for more than 30 years [5].

Adapalene, a synthetic retinoid analogue, is primarily used as a first-line topical retinoid treatment for Acne. It normalizes follicular epithelium cell differentiation and prevents comedone formation. Additionally, it has anti-inflammatory effects on acne lesions.

Tazarotene, a synthetic acetylenic pro-drug, is converted to tazarotenic acid in keratinocytes and is one of the newer retinoids used in acne treatment. It affects keratinocyte differentiation and proliferation in epithelial tissue and may have anti-

inflammatory properties. It is considered a second-line treatment after no response was observed with previous tretinoin or adapalene treatment due to its potential to cause skin irritation in acne patients [48].

Other topical treatments used for acne, such as for example chemical peels, benzoyl peroxide, dapsone, etc. will be discussed in the following section.

Salicylic acid is a keratolytic agent that works by dissolving the intercellular cement that holds the epithelial cells together. It has a minor anti-inflammatory effect and can enhance penetration of certain substances. It is found in various over-the-counter acne treatment products.

Chemical peels (AHA and BHA), which involve the removal of the epidermis, use alpha-hydroxy acids (such as glycolic and lactic acid) and beta-hydroxy acids (such as salicylic acid) to stimulate re-epithelization and skin rejuvenation. Chemical peels can reduce hyperpigmentation and superficial scarring of the skin, but are considered a complementary treatment rather than a first-line option.

Benzoyl peroxide is a topical disinfectant that also works as a comedolytic and antibacterial agent, with no effect on sebum production. It releases free radical oxygen, which degrades bacterial proteins and is effective against P. Acnes [18, 33].

Azelaic acid inhibits protein synthesis of P. acnes, and has bacteriostatic, anti-inflammatory, antioxidant and anti-keratinizing properties. It has not shown bacterial resistance and may be more effective when used with clindamycin, benzoyl peroxide or alpha-hydroxy acids.

Sulfur has mild keratolytic and bacteriostatic properties, but its use in acne treatment has decreased due to its unpleasant odor. It breaks down keratin in the skin and has activity against P. acnes.

Hydrogen Peroxide, *a* study by Tung et al. has shown that a regimen based on hydrogen peroxide for treating mild-to-moderate acne compared well with a regimen based on benzoyl peroxide in terms of cosmetic acceptability, efficacy and safety.

Niacinamide (nicotinic acid) is an active amide of vitamin B3 and is composed of niacin and its amide. It inhibits sebocyte secretions, resulting in less se-

bum production which reduces the oiliness of the skin. In addition to having anti-inflammatory properties which have proved to be beneficial in pustular as well as papular acne. 4% niacinamide has shown significant improvements to acne all over the world [13].

Topical corticosteroids are possible to use under specific circumstances, such as very inflammatory acne. The treatment period should be short and proof of their efficiency should still be determined.

Triclosan, an antibacterial antiseptic, can effectively treat acne without causing bacterial resistance or any expected adverse effects when used as directed.

Sodium sulfacetamide, a sulfonamide antibacterial, inhibits DNA synthesis by competitive antagonism of PABA, and is active against various gram-positive and gram-negative organisms. It is typically only used when other topical agents cannot be tolerated by patients. Dapsone has both antibacterial and anti-inflammatory properties, although its exact mechanism of action against acne is not fully understood. Dapsone gel (5%) can reduce both inflammatory and non-inflammatory acne lesions, and is a cost-effective option for acne treatment in developing countries, but is not recommended as a first-line therapy [49].

Oral systemic treatment is required when acne is resistant to topical treatment or if it manifests as nodular lesions or leaves scarring. This form of treatment is also preferred for treating inflammatory lesions and preventing social and psychological distress caused by acne. The most common forms of systemic treatment include isotretinoin, oral antibiotics, and hormonal agents.

Acne is a common inflammatory skin disease that can cause significant distress for those affected by it. Extensive research has been conducted on the disease itself and available treatment options. The goal of acne therapy is to target the four pathogenic factors responsible for the condition. This review covers various treatment options for acne, including topical and systemic therapies, CAM, and physical treatments. However, due to P. acnes resistance to available antibiotics and individual patient differences, ongoing research in this field will always be necessary.

1.2. Approaches to acne treatment in modern dermatology practice

The major components of the treatment of acne are [7, 9, 14]:

1. Diet (combined with exercise if possible)
2. Topical
3. Systemic
4. Complementary and Alternative Medicines (CAM)

Types of topical retinoids are presented in table 1.1.

Principles Underlying the AACE/ACE Algorithm [35]:

Lifestyle, dietary changes are recommended in the management of acne, recent research suggests that diets with a high glycemic index (GI), which quickly raise blood sugar levels, may have a connection with acne. There is some evidence indicating that specific types of dairy, such as skim milk, may also impact the development of acne.

The main goal of acne treatment is to control and treat existing acne lesions, prevent permanent scarring as far as possible, limit the duration of the disorder and to minimize morbidity. It is important to educate the patient on the goal of preventing new acne lesions while promoting the healing of current ones. Additionally, patients should be informed that it can take anywhere from 3 to 6 weeks before visible improvement is observed [3, 37].

When determining a treatment plan for acne, it is crucial to consider various patient-specific factors, including their current medical condition, disease status, severity of lesions, endocrine history, and preferred treatment approach, be it oral or topical.

Table 1.1

Types and characteristics of retinoids

Retinoids (Mono-therapy)	Plasma half-life	Indica-tions	Contra-indications	Side effects	Trade name/ Available formulations
Tretinoin (all-trans retinoic ac-id)	Normally present in plasma	Acne Vulgaris	Hypersensi-tivity to tret-inoin Pregnancy Nursing	Irritation, local dryness	Stieva-A® cream (tretinoin 0.01%, 0.025%, 0.05%) Retin-A® cream (tretinoin 0.05%) Retin-A® gel (tretinoin 0.025%) Retin-A Micro® gel (tretinoin 0.04%, 0.1%)
Adapalene	7-51 hours (gel)	Acne Vulgaris	Hypersensi-tivity Patients with eczema, seborrheic dermatitis Pregnan-cy/Planning to become pregnant	Irritation Erythema Peeling of the skin Local dryness	Differin® gel (adapalene 0.1%,) Differin® cream (Adapalene 0.1%,) Differin XP® gel (Adapalene 0.3%)
Tazarotene	18 hr (cream, gel)	Plaque Psoriasis Acne Vulgaris	Hypersensi-tivity Pregnan-cy/Planning to become pregnant	Irritation of skin Local dry-ness Erythema Pruritus Worsening of psoriasis	Tazorac® cream (tazarotene 0.05%, 0.1%) Tazorac® gel (tazarotene 0.05%, 0.1%)
Trifarotene	2-9 hours	Acne Vulgaris	Hypersensi-tivity Patients with eczema, seborrheic dermatitis, Pregnan-cy/Planning to become pregnant	Irritation of skin Pruritus	Aklief® cream (trifarotene 0.0005%)

Acne treatment can be administered either topically or systemically, with the latter involving the use of oral drugs. Alternative options include non-drug treatments like optical therapy. However, a combined treatment that addresses multiple mechanisms involved in the pathogenesis of acne is typically more effective. The patient's response to treatment should be carefully monitored, and the regimen adjusted accordingly as their clinical condition improves [10, 23].

Benzoyl peroxide alone or in combination is used with topical antibiotics for mild acne, in combination with topical retinoids or systemic antibiotic therapy for moderate to severe acne.

Retinoids as monotherapy in primarily comedonal acne or in combination with topical or oral antimicrobials in mixed/primarily inflammatory acne

Topical dapsone 5% gel for inflammatory acne, particularly in adult females, Azelaic acid for post-inflammatory pigmentation

Other points of note [24, 50]:

- Benzoyl peroxide does not confer bacterial resistance
- Topical antibiotics are NOT recommended as monotherapy due to risk of bacterial resistance
- Combination therapy should be used in the majority of acne patients to target different aspects of acne pathogenesis
- Patients should be counseled on pregnancy risks when starting a retinoid or if a female patient desires pregnancy
- The topical therapy of acne in children under the age of 12 years with FDA-approved products has expanded
- Benzoyl peroxide 2.5%/adapalene 1% gel – ages 9 and up
- Tretinoin 0.05% micronized gel – ages 10 and up
- The use of topical maintenance regimens after oral antibiotic therapy cannot be overemphasized
- Topical therapies can accomplish continued efficacy months after discontin-

uation of systemic antibiotics.

Topical retinoids play a crucial role in managing acne due to their ability to act against comedones and microcomedones, as well as provide direct anti-inflammatory effects. The substances approved for acne treatment include tretinoin (all-trans-retinoic acid), isotretinoin (13-cis retinoic acid), and the synthetic third-generation polyaromatic retinoids adapalene and tazarotene (the latter being approved for acne treatment in the US only). Retinaldehyde is also used in cosmetic preparations for acne. All topical retinoids are effective as standalone agents in mild to moderate acne, but differ in their efficacy and tolerability. Tazarotene 0.1% is more effective than tretinoin 0.025% or 0.1% microsphere gel or adapalene 0.1% gel or cream. Adapalene 0.1% is equally effective as tretinoin 0.025% or tretinoin microsphere 0.1% gel or tretinoin 0.05% cream or isotretinoin 0.05% gel. Adapalene 0.1% gel is better tolerated than tazarotene 0.1% gel, tretinoin 0.025% and 0.05% gel, tretinoin 0.05% cream, tretinoin microsphere 0.1% gel, or isotretinoin 0.05% gel.

The safety profile of topical retinoids differs from their systemic counterparts, and mainly relates to local adverse effects such as erythema, dryness, itching, and stinging. The currently available evidence supports the use of topical retinoids in most types of acne, including maintenance treatment [38].

Monotherapy:

A study was made to assess the efficacy of topical retinoids as monotherapy in inflammatory acne.

A retrospective, investigator-blinded, vehicle-controlled, photographic assessment study was conducted by five investigators to evaluate the effectiveness of topical retinoids as monotherapy in treating inflammatory acne. The study involved rating pretreatment and posttreatment photographs of patients who had participated in 12- or 15-week double-blind comparisons of tazarotene 0.1% gel, adapalene 0.1% gel, tretinoin 0.1% microsponge, tretinoin 0.025% gel, and tazarotene 0.1% cream (vehicle) on a 7-point acne severity scale. A posttreatment increase or decrease of 1 grade was considered clinically meaningful, while an in-

crease or decrease of ≥2 grades was considered a more significant measure of improvement. The global response to treatment was also rated on a 7-point scale, with a posttreatment increase of ≥2 grades considered clinically relevant improvement.

The study included 577 patients (approximately 52% women and 48% men, with a mean age of 18-20 years), and each of the five investigators rated photographs of all patients, resulting in a total of 2885 evaluations. In addition, 20 control patients were evaluated daily. The treatment groups consisted of tazarotene (252 patients, 1260 evaluations), adapalene (178 patients, 890 evaluations), tretinoin microsponge (47 patients, 235 evaluations), tretinoin gel (39 patients, 195 evaluations), and vehicle (61 patients, 305 evaluations). The results showed that all four retinoids were effective in improving inflammatory acne compared to the vehicle.

In patients with pretreatment acne severity grade ≥3 (mild to moderate), the incidences of clinically significant improvements in the tazarotene, adapalene, and tretinoin microsponge groups were 24%, 17%, and 21%, respectively (all $P \leq 0.001$ vs. vehicle [7%]). The difference in prevalence of clinically significant improvement was statistically similar between the tretinoin gel and vehicle groups. The incidences of clinically relevant improvement in global response to tazarotene, adapalene, tretinoin microsponge, and tretinoin gel were 36%, 34%, 31%, and 28%, respectively ($P \leq 0.001$, ≤ 0.001, ≤ 0.001, and ≤ 0.01, respectively, vs. vehicle [17%]).

Combination Therapy [39]:

Although topical retinoids are the foundation of acne vulgaris treatment, combining them with other anti-acne agents can improve their efficacy. Tazarotene 0.1 percent gel has been shown to be more effective than tretinoin 0.025 percent gel in previous studies, suggesting that tazarotene plus clindamycin may be more efficacious than tretinoin plus clindamycin. A 12-week study randomly assigned 150 patients with facial acne vulgaris to receive either tazarotene 0.1 percent cream plus clindamycin 1 percent gel or tretinoin 0.025 percent gel plus clindamycin 1

percent gel. The tazarotene/clindamycin group had a greater reduction in non-inflammatory and inflammatory lesion counts (71% vs. 52%, p <or =01 and 77% vs. 67%, P=.053, respectively) and a higher incidence of patients achieving> or = 50 percent global improvement (88% vs. 75% at week 12; p <or =.05) than the tretinoin/clindamycin group. Both treatments were equally well tolerated. Due to the complex nature of acne development, multimodal therapy that targets various processes simultaneously has gained attention. Combination products have been shown to be more effective in treating acne and can increase patient adherence by providing personalized treatment options [4].

For moderate to severe acne and less severe inflammatory acne that does not respond to topical therapy alone, it is recommended to combine oral antibiotics, such as doxycycline (more than minocycline or tetracycline), with topical drugs like benzoyl peroxide, azelaic acid, or retinoids. This combination of systemic treatments can reduce the dosage and duration of oral antibiotics, improve patient adherence, increase treatment effectiveness, and decrease the development of bacterial resistance.

Isotretinoin often causes a flare up of acne and therefore it can be combined with corticosteroids for the severe inflammatory acne (abscesses, cysts and nodules)

To enhance the effectiveness of topically applied comedolytic agents, physical removal of microcysts, macrocomedones, or closed comedones is recommended. In addition, the combined use of benzoyl peroxide and salicylic acid has been suggested for the treatment of acne due to their complementary effects, given that they operate through different mechanisms [40].

To assess the safety and efficacy of dapsone gel 5%, an anti-inflammatory agent, in combination with tazarotene cream 0.1% for treatment of acne vulgaris.

In this study, patients were randomly assigned to either receive combination therapy (dapsone gel 5% applied twice-daily and tazarotene cream 0.1% applied daily) or monotherapy (tazarotene cream 0.1% applied daily). The study collected efficacy and safety data at 1, 2, 4, 8, and 12 weeks after treatment. Both groups of

patients (n=86 for dapsone + tazarotene, n=85 for tazarotene) experienced significant reductions in inflammatory, noninflammatory, and total lesion counts (P <001 for all). After 12 weeks, patients treated with dapsone plus tazarotene showed greater reductions from baseline in noninflammatory (comedonal) and total lesion counts than patients treated with tazarotene alone (59.7% vs. 46.5%, P = .01 and 63.3% vs. 53.6%, P = .02, respectively). Additionally, a higher percentage of patients achieved treatment success in the dapsone plus tazarotene group (42.2%) compared to the tazarotene group (21.8%; P = .01). Both treatments were well tolerated.

The results suggest that topical retinoid monotherapy can achieve clinically significant improvements in inflammatory acne.

Combination therapy with dapsone gel 5% plus tazarotene cream 0.1% was more effective than tazarotene monotherapy for treatment of comedonal acne. The results suggest that anti-inflammatory agents such as dapsone can effectively treat early stages of acne (both comedonal and non comedonal) when used in combination with a retinoid [42].

Varients of combination therapy in patients with severe acne is presented in table 1.2.

Table 1.2

Combination therapy in patients with severe acne

#	Varients of therapy
1.	oral isotretinoin
2.	oral isotretinoin + corticoids
3.	high dose of oral antibiotic + topical retinoid
4.	contraceptive/oral antiandrogen (alternative)
5.	topical retinoid + benzoyl peroxide (maintenance)

Oral isotretinoin is the unique treatment for cure or prolonged remission for moderate and severe acne, preventing psychosocial impact and scars. It works by suppressing sebaceous gland activity and has anti-inflammatory and immune-

regulatory effects

Despite common and controllable mucocutaneous side effects, this drug is highly effective. Serious adverse events are rare and typically individual reactions. Teratogenicity is the most severe side effect and requires strict monitoring. Acne recurrence after non-isotretinoin treatments is common, leading to an increased risk of scarring, damage to skin appearance, and emotional distress in young people. Isotretinoin should be considered as the first-line treatment for moderate to severe inflammatory acne unless there is a definite reason to avoid it.

From August 1, 2008, to August 31, 2010, a single academic tertiary care center with multiple providers conducted a prospective, observational, intervention study. The study enrolled 180 patients who had acne resistant to other treatments. Of these, 116 patients participated in the 12-month follow-up survey, resulting in a response rate of 64.4%.

The patients were treated with isotretinoin at a dose determined by the provider. Patients were divided into two groups (<220 mg/kg and ≥220 mg/kg). The study evaluated relapse or retrial at 12-month follow-up and adverse effects experienced during and after 12 months of treatment.

The participants had a mean age of 19.3 years, 51.9% were female, and 74.1% were white. At 12 months' follow-up, 97.4% of the patients reported an improvement in their acne. Overall, 32.7% of patients in the study experienced a relapse at 12 months, and 1.72% of patients required a retrial. In the lower-dose treatment group (<220 mg/kg), the relapse rate was 47.4% compared to 26.9% in the high-dose group (P = .03). Almost all patients in both treatment groups developed cheilitis and xerosis during treatment. Retinoid dermatitis was significantly more common in the high-dose treatment group (53.8% vs. 31.6%; P = .02). None of the other adverse effects were significantly different between the two groups.

The dosing regimen in this study was considerably higher than in previous studies of isotretinoin. The study found that patients receiving 220 mg/kg or more had a significantly decreased risk of relapse at 1 year after completing isotretinoin treatment. Rash was the only adverse effect that was significantly more common in

the high-dose group during treatment. This study suggests that significantly higher doses of isotretinoin can effectively treat acne and reduce relapse rates without increasing adverse effects.

Therapy in patients with moderate acne is presented in table 1.3.

Table 1.3

Therapy in patients with moderate acne

#	Varients of therapy
1.	isotretinoin
2.	topical retinoid + oral antibiotic + benzoyl peroxide
3.	topical retinoid + oral antibiotic + azelaic acid
4.	contraceptive/oral antiandrogen (alternative)
5.	topical retinoid + benzoyl peroxide (maintenance)

The American Academy of Dermatology considered oral antibiotics the main treatment for moderate and severe acne, for over 50 years. In recent years, nevertheless, there has been growing concern regarding the development of antibiotic resistance. As such, some previously employed antibiotics (e.g., erythromycin and clindamycin) are no longer used clinically because of their high rates of resistance. The concern is serious enough that the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) now actively promote campaigns aimed to confront antibiotic resistance.

Oral antibiotics, apart from the tetracycline class (doxycycline, minocycline and sarecycline), are still considered a mainstay of treatment for moderate-to-severe acne because their potential benefits outweigh their potential risks. Although clinical studies and data show that no one antibiotic is superior to another regarding efficacy, safety profiles vary significantly. Efficacy metrics commonly reported in acne studies include the change in inflammatory lesions from baseline to endpoint, the investigator’s global assessment (IGA), which considers acne lesion quality and quantity. While the IGA is a 5 point scale based on acne severity,

results are generally dichotomized into IGA “success” (score of 0 or 1) or IGA «failure» (score >1). Although less common in studies of oral antibiotics, the absolute or percent change in non-inflammatory lesions (open or closed comedones) may also be recorded, as these antibiotics are generally more effective for inflammatory lesions [1, 2, 8].

Monotherapy in patients with mild acne is presented in table 1.4.

Table 1.4

Monotherapy in patients with mild acne

#	Varients of therapy
1.	topical retinoid
2.	topical retinoid + salicylic or azelaic acid
3.	topical retinoid + benzoyl peroxide
4.	topical retinoid + salicylic acid (maintenance)

A recent study has been conducted with a non-prescription acne regimen (Normaderm Phytosolution, Vichy (NP)) which consists of the use of salicylic acid 2%, phyco-saccharide 2%, and vitamin CG in addition to ingredients that enable regeneration of the disrupted skin barrier in acne-affected skin, such as mineralizing water 60%, Bifida ferment lysate 1%, and HA 0.2% in adult females with acne.The exfoliating effect of salicylic acid is similar to natural skin shedding, phyco-saccharide helps to decrease sebum production, and vitamin CG has been shown to have anti-inflammatory properties.The study included 50 women with acne-prone skin having at least 5 inflammatory acne lesions and 10 non-inflammatory lesions as well as a dull and uneven complexion. The study evaluated skin condition, sebum tape, and pH measurements, and subjective assessment of the skin complexion radiance, homogeneity, and patient satisfaction with the treatment. The women used the NP regimen twice daily for eight weeks and had a significant ($P< 05$) reduction of the number of inflammatory lesions (papules and pustules), non-inflammatory lesions (open and closed comedones), erythematous

macules, and pigmentation evaluated by a dermatologist. Patients reported a high degree of satisfaction with the treatment. A study that has not been published yet examined the impact of a skincare routine containing mineralizing water (60%), Bifida ferment lysate (1%), and HA (0.2%) on the quality of life of 232 women from diverse ethnic backgrounds, including African (24.8%), Asian (24.8%), Caucasian (25.6%), and Hispanic (24.8%) participants. The women who had oily and acne-prone skin reported improvements in their skin condition, behavioral aspects, and emotional status after using the skincare regimen daily for eight weeks. The findings of the study suggest a significant positive effect on the participants' well-being.

Tretinoin, Adapalene, Tazarotene, Trifarotene, and oral Isotretinoin, are FDA-approved for acne treatment. Tazarotene is also approved for the treatment of plaque psoriasis on up to 20 percent of body surface area. As retinoid use is limited by irritation, treatments are available in multiple dosages and formulations (i.e., cream, oil, gel, lotion). Studies have shown that topical tazarotene is safe and effective for the treatment of psoriasis (dosages: 0.1%; 0.01%; 0.05%; 0.045%) and acne (0.1%; 0.05%; 0.045%). As acne is a very common disease in women of child-bearing age and topical retinoids are a typical treatment, it is possible for women to be exposed to a topical retinoid during pregnancy.

The most commonly available topical retinoids are tretinoin, adapalene and tazarotene. A meta-analysis of five multicentre trials involving 900 patients showed Adapalene 0.1% gel to be as effective as, and less irritating than, tretinoin 0.025% gel. Different concentrations of retinoids affect tolerability. One commonly used approach is to start with the lowest concentration and increase as tolerated.

Tazarotene therapy:

Low systemic exposure to a drug may reduce the potential risk of teratogenicity. Topical tazarotene has a low systemic exposure which means limited percutaneous penetration, rapid metabolism to hydrophilic metabolites (preventing accumulation in adipose tissue), and rapid elimination. Tazarotene has a mean half-life of 17 to 18 hours. Systemic bioavailability with 0.1% monotherapy dosing

was 1% in healthy participants after single and multiple applications; in patients with psoriasis, bioavailability was one 1% and there was an increase 5% by Week 2, but this decreased by Week 12. This increase in bioavailability may have been due to a compromised epidermal barrier that occurs in patients with psoriasis; in addition, initial tazarotene treatment can thin psoriatic plaques and further reduce the skin barrier. After 12 weeks, skin barrier properties may have been restored, reducing permeability to tazarotene. In patients with acne and psoriasis treated with 0.1% tazarotene cream, tazarotenic acid plasma levels were similar to endogenous retinoid levels measured in healthy volunteers and lower than in healthy volunteers dosed with vitamin A. Single 40 mg or 80 mg doses of oral isotretinoin, by comparison, had similar or slightly longer half-lives of 18 or 21 hours than topical tazarotene but 30 to 70 times greater mean plasma concentrations, respectively. Overall, these data indicate that systemic exposure from topical tazarotene 0.1% is generally low and similar to endogenous retinoid levels.

Although topical retinoids have been shown to have a positive safety profile and provide minimal systemic exposure in clinical trials for acne and psoriasis, the use of oral or topical retinoids during pregnancy is not advised. Studies conducted on rats and rabbits have revealed retinoid-related malformations and developmental delays in their offspring when given oral retinoids during pregnancy. There have also been instances of retinoid-linked abnormalities in humans. Isotretinoin, an oral retinoid approved by the FDA for the treatment of severe and persistent nodular acne in 1982, has been linked to significant congenital malformations, some of which have resulted in death, in children exposed in utero. Women who use isotretinoin during pregnancy are also at an elevated risk of spontaneous abortions and premature births. Tazarotene, a retinoid available in both oral and topical forms, has demonstrated teratogenic effects in pregnant rats and rabbits given doses above the maximum recommended human dose. However, it is uncertain what level of exposure could result in teratogenicity in humans.

Conclusions for chapter 1

1. Acne has high prevalence in the world and the amount of patients is growing continuously.
2. The most frequently prescribed topical retinoids are tretinoin, adapalene and tazarotene, which resembles the Food and Drug Administration (FDA), but can be associated with side effects.
3. There is a significant gap between the beliefs and understanding of the efficiency criteria for acne treatment and factors that are important for its success from dermatologists and patient’s perspectives.

CHAPTER 2
MATERIALS AND METHODS

The experimental part of the master thesis was conducted in collaboration with Atlas pharmacy, El jadida, Morocco.

For the purposes of the master thesis a questionnaire was developed for surveying of pharmacy visitors with acne (table. 2.1.)

This chapter included questions concerning the criteria of efficiency of the treatment of acne as well as the safety, that from the point of view of the pharmacy visitor are the most important for the effectiveness of the treatment.

The study was conducted in the period from February 20, 2023 to March 05, 2023. Our study included pharmacy customers who were/are using combination topical acne therapy.

The questionnaire included questions of a general nature regarding the age, gender, professional activity of the respondent, as well as special questions related directly to the features of the local acne therapy being carried out. Particular attention was also paid to the assessment of indicators of the quality of life of patients with acne.

Also, based on the results of the survey, practical recommendations were developed to improve the efficiency and safety of local acne therapy using modern therapeutic possibilities of combination therapy. We have formulated the principles of pharmaceutical care when using topical acne treatments, which are of practical importance not only for patients with acne, but also for medical and pharmaceutical specialists.

The methodological basis of the study is the principles of objectivity and consistency. The work uses a complex of general scientific and special methods: theoretical, generalization, data systematization, comparison, methods of studying literary sources, analysis, questionnaire method, statistical methods, etc.

Table 2.1

Questionnaire for pharmacy visitors with acne

Sex + age
Family history + age where acne first started
How severe is the acne from scale 1 to 10?
What are the factors that worsen acne?
What skin care did you use and how often?
What treatment is used? 1. Is it effective? 2. Is it safe? 3. For how long? 4. Are you satisfied with the results ?
Did you have any allergic reaction to any of the products ?
Did the treatment cause any skin problems such as: 1. Dryness or Oiliness 2. Pain or itching 3. Sensitivity
Is there an improvement or worsening since starting any medication ?
Do you have any lifestyle that contributes to acne breakout? 1. Stress 2. Smoking 3. Alcohol consumption 4. Lack of sleep 5. Medication
Have you tried any OTC medication? Was it effective ?
What do you think about acne? How does acne impact your life?

Conclusions for chapter 2

1. The questions concerning the criteria of efficiency of treatment and about the factors, that from the point of view of the pharmacy visitor, are the most important for the effectiveness of the treatment. In the questionnaire for pharmacy visitors the questions and answers were adopted for better understanding by pharmacy visitors.

2. For the purposes of the survey were pooled 25 pharmacy visitors who presented in Atlas Pharmacy, El Jadida.

CHAPTER 3
IMPROVING MEDICATION ADHERENCE FOR ACNE MANAGEMENT

3.1 Survey of patients with acne vulgaris concerning efficiency of treatment using retinoids

The total number of surveyed pharmacy visitors was 25. The inclusion criteria were: diagnosis with acne, use of at least 1 retinoid (topical or oral); volunteering to take part in the survey.

The main characteristics of the surveyed pharmacy visitors are presented in the table 3.1.

Table 3.1

Characteristics of surveyed pharmacy visitors

#	Patients characteristics	Indicator	% from total amount
1.	Sex		
	Female	19	76
	Male	6	24
2.	Minimal age, years	15	
3.	Maximal age, years	33	
4.	Pharmacy visitors, that take more than 1 medication	5	20
5.	Acne severity: Mild Moderate Severe	9 10 6	36 40 24
6.	Total amount of pharmacy visitors surveyed	25	100

From all surveyed pharmacy visitors, 19 are females (76%) and 6 are male (24%). The average age was 33 ± 15 years, the youngest respondent was 15 years

old and the oldest – 33 years old. The prevalence of acne starts between the ages of 11 and 20. From all surveyed pharmacy visitors 20% take more than one medication (5 respondents). A total of 40% of patients had moderate acne, 36% mild acne and 24% severe acne.

Table 3.2

Factors, that lead to higher acne breakouts

#	Factor	Total amount	%
1.	Diet (diary, chocolate, fast food, greasy food)	23	92
2.	Stress	22	88
3.	Sleep disorders	16	64
4.	Smoking	3	12
5.	Alcohol consumption	11	44
6.	Medication (birth control or other)	5	20

According to the survey results (table 3.2), following the dietary recommendations was marked by almost all respondents as an important factor for the effectiveness of acne treatment (22 patients, 92%). Stress is also an important factor, 88% of respondents complained of stress as one of the main triggers of breakouts (22 patients). Lack of sleep impacted acne breakouts as indicated by 16 patients (64%) (as it increases stress levels). The Factor alcohol consumption was signaled by 11 patients which include (44%), the factors smoking and medications were the least influential in the opinion of patients, smokin by 3 patients (which is 12%) and Medications by 20% of them (5 patients).

The survey results concerning drugs used by patients with acne and their efficiency are presented in the table 3.3.

Table 3.3

Characteristics of medicines used by surveyed pharmacy visitors

Medications	Dosage form	Group of medication	Severity of acne
Differin (Adapalene)	Gel Cream	Topical retinoid	Mild
Cutacnyl (Benzoyl Peroxide)	Gel	Antiinflammatory topical antibiotic	Mild Moderate
Retacnyl (Tretinoin)	Cream	Topical retinoid	Mild Moderate
Curacne (Isotretinoin)	Tablet	Retinoids	Severe
Roaccutane (Isotretinoin)	Tablet	Retinoids	Severe
Doxymycine (Doxycycline)	Tablet	Antibiotic (Tetracyclines)	Moderate
Tetralysal (Lymecyclin)	Tablet	Antibiotic (Tetracycline)	Moderate
Dalacine (Clindamycin) Clindac A	Tablet Gel	Topical antibiotic	Moderate severe
Eryfluid (Erythromycin)	Gel	Antibiotic (Macrolide)	Mild Moderate

Different groups and forms of medications are used in the treatment, depending on the severity of the acne. For mild acne adapalene or tretinoin are used the most, it is preferable to use adapalene as it is the safest, benzoyl peroxide and erythromycin are also used especially for maintenance and prevention of acne in both mild and moderate acne.

For moderate acne, the use of antibiotics in addition to topical retinoids is very common, mostly doxycycline, lymecyclin, clindamycin which can also be used in severe cases and erythromycin that can be effective in cases of mild acne.

For severe acne oral isotretinoin is the best option, despite the intensity and hardness of the treatment, and the side effects.

The survey results of the use of topical retinoids are presented in Figure 3.1.

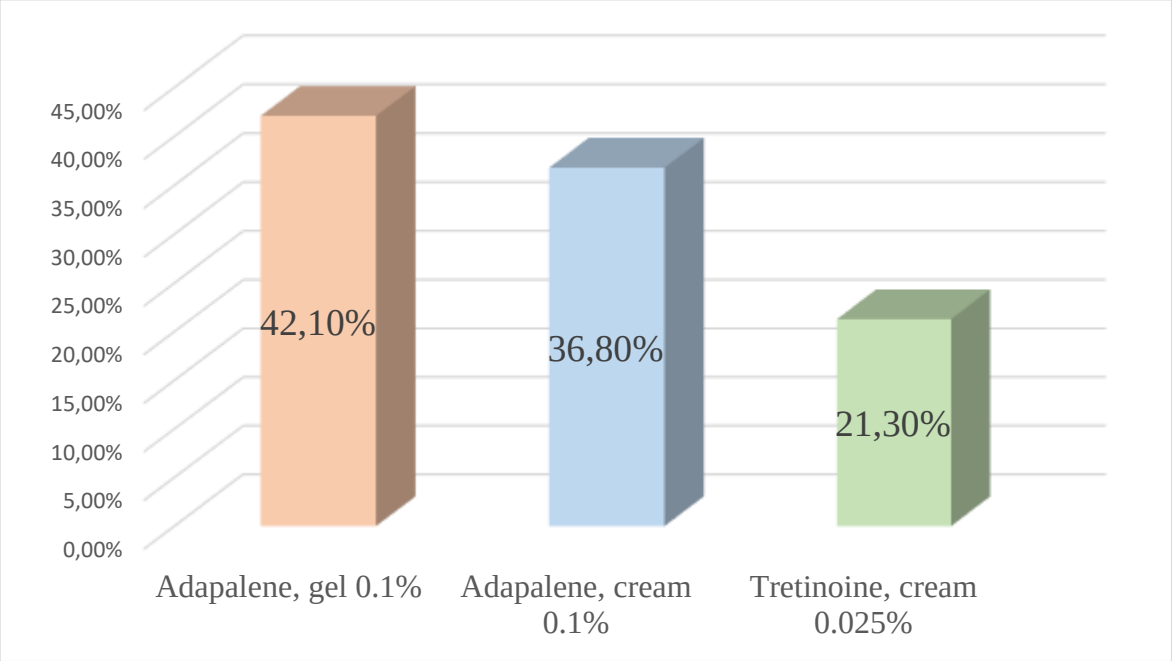

Fig. 3.1. Analysis of topical retinoids use

Adapalene gel has a waterier consistency and dries quickly, making it suitable for oily skin types, it was used in 42.1% of the cases, while adapalene cream used in 36.8% cases is thicker and more moisturizing, making it suitable for sensitive and drier skin types. The main difference between tretinoin cream and adapalene products is the strength and potency of the medication. Tretinoin is generally considered to be stronger and more potent than adapalene, which can make it more irritating to the skin, particularly for people with sensitive skin.

According to the survey results (table 3.4), the most efficient are adapalene and tretinoin, by a rate of 100% efficacy, then Isotretinoin with only 1 patient unsatisfied wich leaves it at 83%, after that BP with a rate of 75% and clindamycin and erythromycin with a 66 % success rate, then lymecycline was efficient in half the cases, and the least efficient is doxycycline with the rate of 40% which makes it efficient in 2 cases out of 5.

Table 3.4

Factors, that indicate the effectiveness and safety of treatment (pharmacy visitors perspective)

Medications	Number of users	Efficacy, % of cases
Differin (Adapalene)	15	100 %
Cutacnyl (Benzoyl Peroxide)	4	75%
Retacnyl (Tretinoin)	5	100%
Curacne (Isotretinoin) Roaccutane	6	83%
Doxymycine (Doxycycline)	5	40%
Tetralysal (Lymecycline)	2	50%
Dalacine (Clindamycin) Clindac A	3	66%
Eryfluid (Erythromycin)	3	66%

The survey results concerning the use of topical retinoids and antibiotics, topical and oral are presented in Figure 3.2.

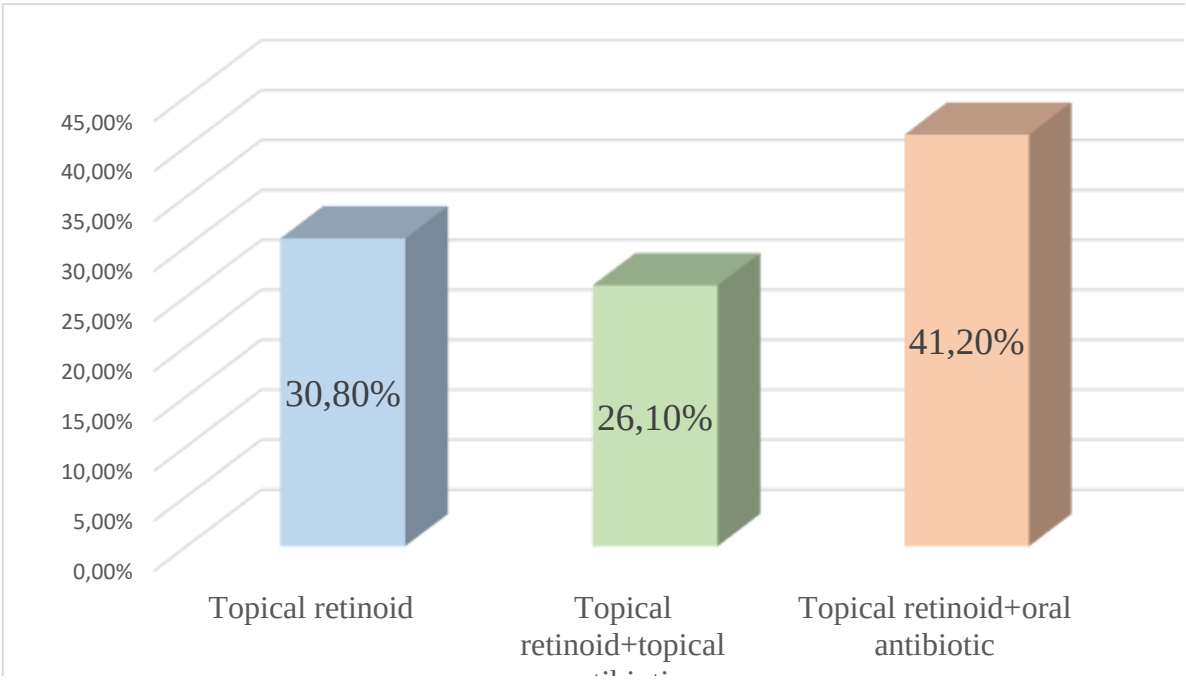

Fig. 3.2. The use of topical retinoids and antibiotics, topical and oral

The survey results concerning the side effects and recommendations are presented in table 3.5.

Table 3.5

Side effects and recommendations by pharmacy visitors with acne

Medications	Side Effects
Differin (Adapalene) Cutacnyl (Benzoyl Peroxide)	Common side effects include dryness, redness, itching, burning, and stinging of the skin
Retacnyl (Tretinoin)	Common side effects include dryness, redness, burning, stinging, and itching of the skin. It can also cause increased sensitivity to sunlight
Curacne (Isotretinoin) Roaccutane	Serious side effects may include birth defects, depression, suicidal thoughts, liver damage,joint pain, an increased risk of inflammatory bowel disease, extreme dryness of skin and lips, burning sensation, flaking of skin, , and increased sensitivity to sunlight
Doxymycine (doxycycline) Tetralysal (Lymecycline)	Common side effects include nausea, vomiting, diarrhea, and loss of appetite. It can also cause skin rash, sensitivity to sunlight, and vaginal itching or discharge
Dalacine (Clindamycin) Clindac A Eryfluid (Erythromycin)	Common side effects include dryness, itching, and redness of the skin. It can also cause skin rash, stomach pain, diarrhea, and changes in bowel habits

The side effects of the acne medications listed above are generally mild to moderate and are mostly related to the skin and gastrointestinal tract. Some medications may cause increased sensitivity to sunlight, so it's important to take appropriate sun protection measures, moisturize and increase water consumption. However, isotretinoin (Curacne, Roaccutane) has some serious potential side effects,

such as teratogenicity, depression, suicidal thoughts, and liver damage. It should only be used under close medical supervision and with appropriate monitoring.

Additionally, antibiotics such as doxycycline, lymecycline, clindamycin, and erythromycin can contribute to the development of antibiotic resistance with long-term use. Therefore, it's important to use these medications only as prescribed by a healthcare provider and to follow up regularly to monitor their effectiveness and side effects. As with any medication, individuals may have different reactions to acne treatments.

Survey results concerning the most common side effects following the use of topical retinoids in Figure 3.3.

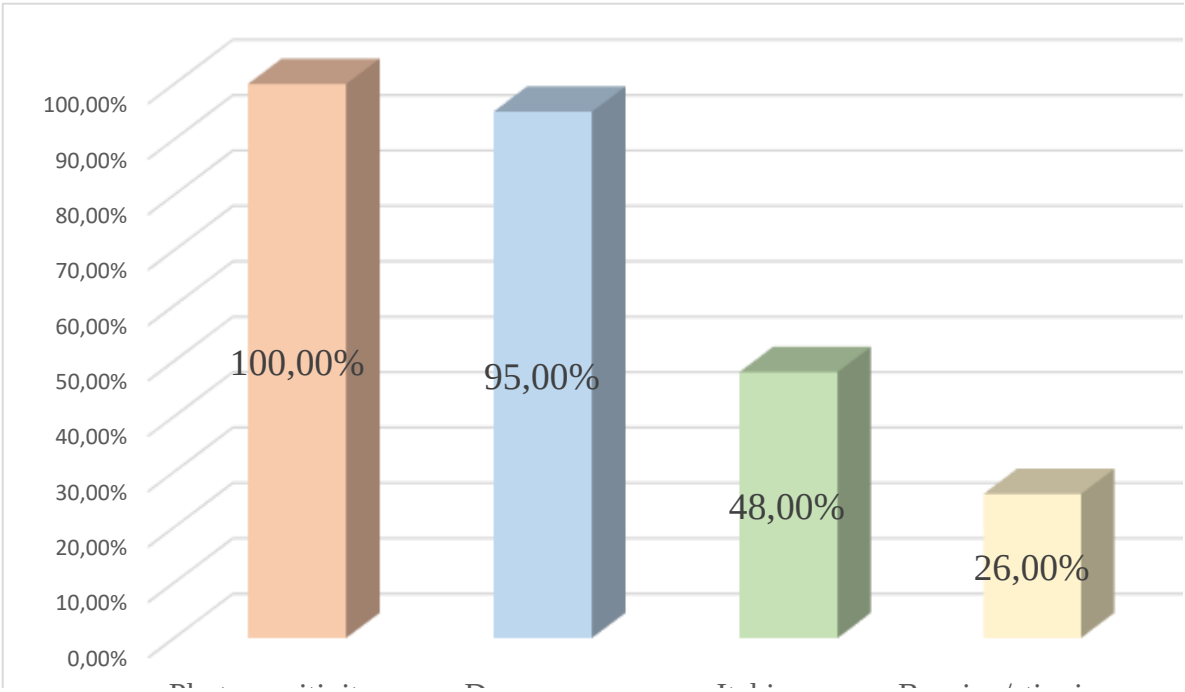

Fig.3.3. The most common side effects following the use of topical retinoids

Photosensitivity and dryness are very common and predictable side effects with a percentage of 100% and 95%, as long as it is tolerable, it doesn’t preclude the use of topical retinoids, this applies equally for itching which was in 48% of cases and burning or stinging sensation in 26% of cases.

Skin care plays an important role in both the prevention and treatment of acne. The main of them are presented in table 3.6.

Table 3.6

Products, that are most important for the maintenance of skin during and after treatment (pharmacy visitor's perspective)

Cleanser	Moisturizer	Serum / peeling	Sunscreens
CeraVe Acne Foaming Cream Cleanser	Liquid Exfoliant CeraVe Facial Moisturizing Lotion	Paula's Choice Skin Perfecting 2% BHA	EltaMD UV Clear Broad-Spectrum SPF 46
La Roche posay Effaclar Medicated Gel Acne Face wash	La Roche Posay Toleriane Double Repair Face Moisturizer	La Roche Posay Effaclar Adapalene Gel	La roche-Posay Anthelios spf 50
Cetaphil face wash	Cetaphil Moisturizing Lotion	The Ordinary Niacinamide 10% + Zinc 1%	Isdin Fusion Fluid MINERAL spf 50
Vichy Normaderm Phytosolution Purifying Gel	Vichy Normaderm anti-imperfection hydration 24h	The ordinary 7% Glycolic acid peeling	Vichy Capital idéal soleil spf 50
Sensilis gentle cleansing foam	Dermopure skin renewal treatment 10% Hydroxy complex	Eucerin dermopure	Eucerin Photo-aging control Spf50

Skin care plays an important role in both the prevention and treatment of acne. Proper skin care can help to reduce oil production, remove dead skin cells, and unclog pores, all of which can help to prevent new acne lesions from forming. It can also help to reduce inflammation and speed up the healing process of existing acne lesions.

While there are a variety of gentle cleansers, moisturizers, and photoprotective formulations to choose from, there is a lack of research on how specific skin care products, particularly cleansers, moisturizers, and photoprotectants, impact individuals with acne who are undergoing treatment, as well as those who are not. Furthermore, there is a shortage of well-conducted studies comparing the benefits and drawbacks of specific formulations and ingredients.

Comparison of the number of cases that were treated in the pharmacy and the number of cases treated by a doctor are presented in Figure 3.4.

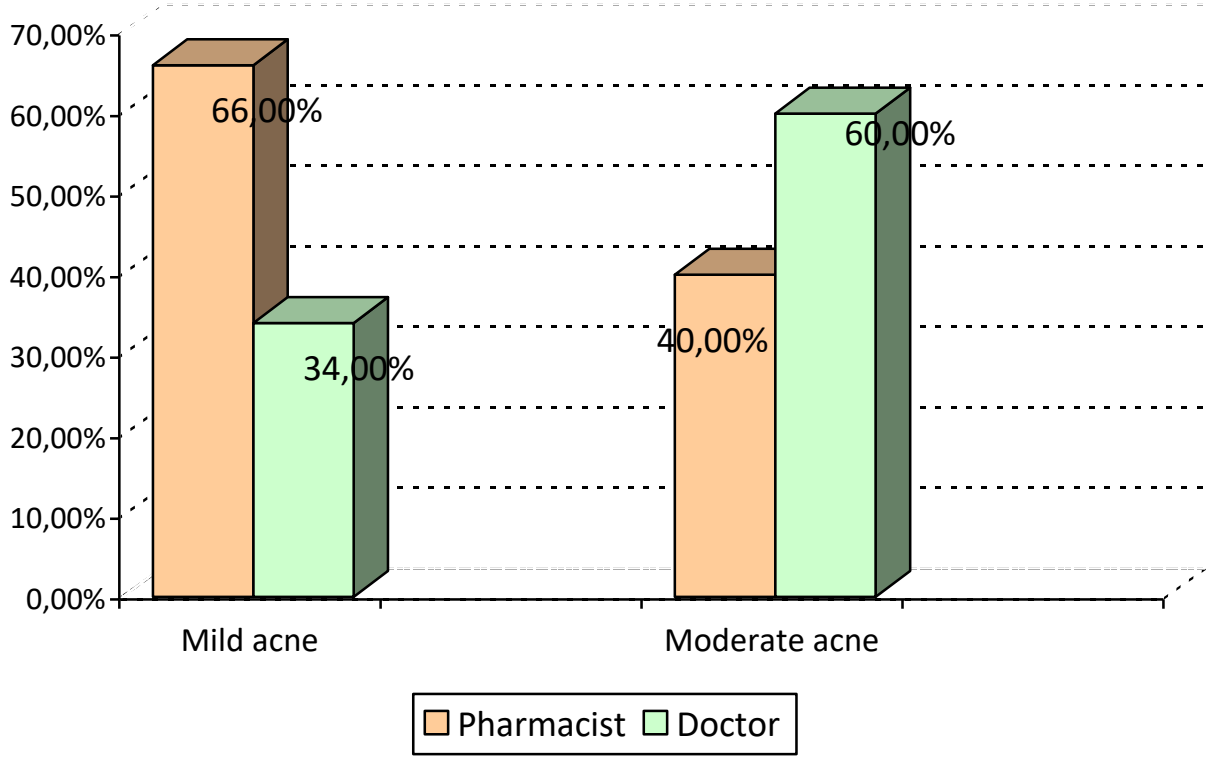

Fig. 3.4. Percent of cases treated by doctors and pharmacists

In the research conducted 66% of patients with mild acne were treated in the pharmacy and 33% had a prescription from a doctor. While those with moderate acne 40% were treated by a pharmacist and 60% by a doctor.

3.2 Discussion of the obtained results

The consensus among all patients was that acne can have a significant impact on a person's physical appearance, self-esteem, and overall quality of life. Acne can range in severity from mild to severe and can manifest in different forms such as blackheads, whiteheads, pimples, and cysts. It is crucial for the patient to identify the triggers which can be some type of food, smoking and alcohol consumption, sleep disorder, some type of medication or stress in order to stop worsening the acne.

Then comes the treatment, which can be topical, oral or both depending on the severity of acne, for Mild acne which is mostly whiteheads and blackheads, with a few papules and pustules, the best treatment option would be topical retinoids, which can be diagnosed and supervised by a pharmacist, the patient should be aware of the side effects those type of medications can cause including redness, itchiness, photosensitivity and sometimes stinging of the skin.

In case of moderate acne, which include multiple papules and pustules, along with occasionally inflamed nodules, should be examined and supervised by a dermatologist, the treatment usually includes an antibiotic, oral or topical and a topical retinoid. The duration, doses and the choice of medication depend on each case individually. The side effects in this case can be more intense, as they may include nausea, vomiting, diarrhea, and loss of appetite as well as skin rash, sensitivity to sunlight, and vaginal itching or discharge.

Lastly, for severe cases also supervised by a dermatologist, in the presence of cystic, large, painful and inflamed pustules and nodules, a heavy treatment takes place with an oral retinoid, that involves extreme dryness of the skin, chapped lips, dry eyes, photosensitivity, peeling of the skin and nosebleeds in some cases. As for the possible side effects, there is depression, liver damage, joint pain, and an increased risk of inflammatory bowel disease as well as a teratogenic effect.

In summary, acne treatment is essential to prevent scarring, improve self-esteem, and reduce emotional distress associated with the condition. Seeking pro-

fessional treatment and taking steps to manage acne can greatly improve a person's overall quality of life.

3.3 Practical recommendations for pharmacists

Understanding the pathology is crucial in any treatment, it is up to the health workers (Pharmacists in this case) to communicate in an efficient way information about the disease, the treatment and do follow ups.

The pharmacist should be able to assess the severity of the acne: Mild, Moderate or severe. Assess the patient's acne to determine the appropriate treatment plan. Mild acne can often be treated with over-the-counter products that should be under the provision of the pharmacist while moderate to severe acne may require prescription medications, but the pharmacist is still under the obligation to:

Educate patients about the causes of acne: Acne is caused by a combination of factors, including hormonal changes, excess oil production, and bacterial growth. Explain to patients that acne is a common condition that can be treated effectively with the right approach.

Recommend over-the-counter products that contain ingredients such as salicylic acid, benzoyl peroxide, or alpha-hydroxy acids. These products can help to unclog pores and reduce inflammation.

Discuss prescription options: If the patient has moderate to severe acne, discuss prescription options with them. Prescription medications such as topical retinoids, antibiotics, or hormonal therapies can be effective in treating acne.

Encourage good skincare habits: Good skincare habits can help to prevent acne and improve the appearance of existing acne. Encourage patients to wash their face twice a day with a gentle cleanser, avoid picking at acne lesions, and use non-comedogenic moisturizers.

Advice on lifestyle factors: Certain lifestyle factors can contribute to the development of acne. Encourage patients to maintain a healthy diet, get regular exercise, and manage stress levels.

Follow up with patients: Follow up with patients to ensure that their acne treatment is working effectively. Adjust the treatment plan as needed to achieve the best possible outcome.

Conclusions for chapter 3

1. Diet plays an important role in the control of acne, stated by 92%. Stress is also an important factor, (88%) of respondents complained of stress as one of the main triggers of breakouts. Lack of sleep was indicated by (64%) patients. Alcohol consumption was signaled by (44%), while smoking and medications were the least influential in the opinion of patients, smoking patients (12%) and medications consumers by 20% of them.

2. The efficacy of treatment changed from a patient to another, according to the survey results, the most efficient are Adapalene and Tretinoin, by a rate of 100% efficacy, then Isotretinoin by 83%, after that BP and Clindamycin and Erythromycin with a rate of 66 % efficacy rate, then Lymecycline that was efficient in half the cases studied, and the least efficient is Doxycycline with the rate of 40%.

3. Skin care was different from one patient to another, it is up to the dermatologist to determine which products would be more suitable for each individual case.

4. Pharmacists were able to treat 66% of cases of mild acne, and 40% of moderate acne while 33% of patients with mild acne and 60% with moderate acne preferred to go to a doctor for the diagnosis and treatment.

CONCLUSIONS

1. Acne vulgaris is one of the most well-known and common skin conditions. It affects people of all ages.

2. The most frequently used treatments are topical retinoids and antibiotics as well as systemic retinoids and antibiotics.

3. Lifestyle plays an important role in management and control of acne. Diet control affirmed by 92%. Stress is also an important factor, (88%) of respondents complained of stress as one of the main triggers of breakouts; 64% confirmed that lack of sleep is the cause. Alcohol consumption was signaled by (44%), while smoking and medications were the least influential in the opinion of patients, smoking patients (12%) and medications consumers by 20% of them.

4. According to the survey, not all pharmacy visitors were satisfied with results, the most efficient are adapalene and tretinoin, by a rate of 100% efficacy, then isotretinoin by 83%, after that BP with a 75% rate, clindamycin and erythromycin with a rate of 66 % efficacy, then lymecycline and that was efficient in 50% of the cases, and the least efficient is doxycycline with the rate of 40%. As most patients would not see any major improvement.

5. Skin care plays an important role in the maintenance and protection of skin. Some products containing benzoyl peroxide, salicylic acid, glycolic acid and those containing AHA and BHA prevent clogging of pores and reduce the oiliness of the skin and thus prevent acne. Protection is also crucial in the treatment of acne, as most medications make the skin photosensitive, a good sunscreen, broad spectrum and Spf 50 would be very helpful.

6. The role of the pharmacist in acne treatment includes explaining more about the pathology, discussing the treatment options, giving advice for better care, doing follow ups and most importantly giving the treatment to those who can be treated by OTC drugs.

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Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of clinical pharmacology and clinical pharmacy

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
Acting Head
of Department
of Clinical Pharmacology
and Clinical Pharmacy

Tetiana SAKHAROVA
«02» of September 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Ikram AGOUNTAF

1. Topic of qualification work: «Optimizing the use of topical retinoids in Moroccan patients with acne», supervisor of qualification work: Inna OTRISHKO, PhD, assoc. prof.

approved by order of NUPh from «06th» of February_2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: April 2023.

3. Outgoing data for qualification work: adherence, acne, topical retinoids, healthcare providers, efficacy and safety of therapy, quality of life.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): to conduct a literature review on the treatment of acne; to analyze the issues of adherence to topical retinoids therapy; develop a questionnaire for patients; conduct questionnaires and process experimental data; develop practical recommendations to the rational use of topical retinoids.

5. List of graphic material (with exact indication of the required drawings):
tables – 11, figures – 4.

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1.	Inna OTRISHKO, associate professor of higher education institution of clinical pharmacology and clinical pharmacy department	02.09.2022	02.09.2022
2.	Inna OTRISHKO, associate professor of higher education institution of clinical pharmacology and clinical pharmacy department	02.09.2022	02.09.2022
3.	Inna OTRISHKO, associate professor of higher education institution of clinical pharmacology and clinical pharmacy department	02.09.2022	02.09.2022

7. Date of issue of the assignment: «02» September 2022

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Conducting a literature review on the issues of the work.	September-November 2022	**done**
2.	Conducting a survey of endocrinologists and patients.	December 2021	**done**
3.	Experimental data processing.	January-February 2023	**done**
4.	Writing the qualification work.	March-April 2023	**done**
5.	Registration of the work and accompanying documents and submission to the Examination Committee of the NUPh.	April 2023	**done**

An applicant of higher education _____ Ikram AGOUNTAF

Supervisor of qualification work _____ Inna OTRISHKO

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **кафедри клінічної фармакології та клінічної фармації**				
Ахуттаф Ікрам	Оптимізація застосування топічних ретиноїдів у марокканських пацієнтів з акне	Optimizing the use of topical retinoids in Moroccan patients with acne	доцент Отрішко І.А.	професор Бутко Я.О.,

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу

щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

№ 113059 від « 5 » травня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Агунтаф Ікрам, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Оптимізація застосування топічних ретиноїдів у марокканських пацієнтів з акне / Optimizing the use of topical retinoids in Moroccan patients with acne», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
професор **Інна ВЛАДИМИРОВА**

0%

26%

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Ikram AGOUNTAF

on the topic: «Optimizing the use of topical retinoids in Moroccan patients with acne»

Relevance of the topic. Acne is a chronic, inflammatory disease of the pilosebaceous unit estimated to affect 9.4% of the global population. Many treatments for acne are currently available; guidelines recommend a combination of a topical retinoid and an antimicrobial agent for most patients with acne in order to target both inflammatory and non-inflammatory lesions. Although acne typically requires prolonged treatment, poor adherence to acne therapies has been documented.

Practical value of conclusions, recommendations and their validity. The research conducted in this work is the basis for further clinical and pharmaceutical studies, development and implementation of principles for optimizing the use of topical retinoids. The implementation of these principles and provisions in practical medicine and pharmacy will help to increase the effectiveness and safety of acne treatment.

Assessment of work. The work is performed at a sufficient scientific and methodological level. In terms of relevance, scientific novelty and practical significance, it fully meets the requirements for qualification works.

General conclusion and recommendations on admission to defend. The work is performed in full, designed in accordance with the current requirements for the qualification works at the National University of Pharmacy and can be recommended for submission to the EC for further defense.

Scientific supervisor _____ Inna OTRISHKO

«11» April 2023

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Ikram AGOUNTAF

on the topic: «Optimizing the use of topical retinoids in Moroccan patients with acne»

Relevance of the topic. Acne vulgaris is the most common dermatological disorder globally in the world, with an estimated prevalence of 650 million adolescents and adults affected. Current acne treatment recommendations are dependent on the severity of the condition identified by different gradings. Systemic and topical medications, such as retinoids, topical antibiotics, and benzoyl peroxide, are associated with skin barrier alteration, and may be associated with skin dryness and irritation in some patients.

Theoretical level of work. The literature review conducted on the subject of the study illustrates the state of medication adherence of patients today and outlines the prospects for research in this area.

Author's suggestions on the research topic. The provisions of the author of the work on medication adherence are of practical importance for the modern health care system.

Practical value of conclusions, recommendations and their validity. According to the results of research, approaches to the rational use of topical retinoids for different categories of patients with acne have been developed. The author discusses the main approaches to increase the medication adherence in acne patients. Practical recommendations for all healthcare providers are proposed.

Disadvantages of work. Single grammatical and spelling errors do not affect the overall positive assessment of the work.

General conclusion and assessment of the work. The work meets the requirements for qualification work in NUPh and can be recommended for defense.

Reviewer _____ prof. Yaroslava BUTKO

«15» April 2023

МОЗ України
Національний фармацевтичний університет

ВИТЯГ З ПРОТОКОЛУ №10

Засідання кафедри клінічної фармакології та клінічної фармації

м. Харків «19» квітня 2023 р.

СЛУХАЛИ: Про представлення до захисту в Екзаменаційній комісії випускної кваліфікаційної роботи на тему: **«Оптимізація застосування топічних ретиноїдів у марокканських пацієнтів з акне» / «Optimizing the use of topical retinoids in Moroccan patients with acne»**

здобувача вищої освіти 5 курсу, спеціальність – 226 Фармація, промислова фармація, освітня програма – Фармація, ступінь вищої освіти – магістр, термін навчання – 4 р. 10 міс., денна форма навчання, НФаУ 2023 року випуску

Агунтаф Ікрам

прізвище, ім'я та по батькові

Керівник: доцент закладу вищої освіти кафедри клінічної фармакології та клінічної фармації, к.фарм.н., доцент Отрішко І.А.

Рецензент: професор закладу вищої освіти кафедри фармакології та фармакотерапії, д.фарм.н., професор Бутко Я.О.

В обговоренні кваліфікаційної роботи брали участь:

В.о. зав. кафедри, професор Т.С. Сахарова; професор В.А. Мороз; професор С.К. Шебеко; доцент О.О. Андрєєва; доцент Н.П. Безугла; доцент В.В. Пропіснова; доцент С.В. Місюрьова; доцент І.А. Отрішко; доцент О.О. Тарасенко; доцент К.М. Ткаченко; асистент С.М. Зімін; асистент Т.С. Жулай; асистент Н.В. Давішня; асистент Т.Ю. Колодєзна; асистент К.В. Вєтрова; асистент Ю.В. Тимченко

ПОСТАНОВИЛИ: Рекомендувати до захисту в ЕК кваліфікаційну роботу здобувача вищої освіти

Агунтаф Ікрам

прізвище, ім'я та по батькові

На тему: **«Оптимізація застосування топічних ретиноїдів у марокканських пацієнтів з акне» / «Optimizing the use of topical retinoids in Moroccan patients with acne»**

В.о. завідувача кафедри _____ Тетяна САХАРОВА
(підпис)

Секретар _____ Катерина ТКАЧЕНКО
(підпис)

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Ікрам АГУНТАФ до захисту кваліфікаційної роботи

за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Оптимізація застосування топічних ретиноїдів у марокканських пацієнтів з акне» / «Optimizing the use of topical retinoids in Moroccan patients with acne».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Ікрам АГУНТАФ виконав весь необхідний обсяг робіт. Кваліфікаційна робота може бути рекомендована до подачі в ЕК НФаУ для подальшого її захисту.

Керівник кваліфікаційної роботи

_____ Інна ОТРІШКО

«11» квітня 2023 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Ікрам АГУНТАФ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

В.о. завідувача кафедри
клінічної фармакології та клінічної фармації

_____ Тетяна САХАРОВА

«19» квітня 2023 року

Qualification work was defended
of Examination commission on
«___» June 2023
with the grade _____

Head of the State Examination commission,
DPharmSc, Professor
_____ / Oleh SHPYCHAK /