Acne in the Adult

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Abstract: This paper is a general overview that contributes for the knowledge systematization concerning the characteristics of the acne in the adult, its prevalence, causes, diagnosis, classification and drugs available for treatment. The reference therapy is the combination between topical retinoids and oral antibiotics. Oral isotretinoin is still the only available therapy that may modify the different acne physiopathologic factors and therefore it is the standard treatment for severe acne. The importance of the acne treatment in the adult should be enhanced as it can also lead to symptoms of serious depression and anxiety.

Key Words: Acne, adult, hormones, prevalence, physiopathology, retinoids, antibiotics, chemical structures.

INTRODUCTION: ACNE AND THE PATIENTS´ QUALITY OF LIFE

A sudden interest for acne in the adult has been appearing, and consequently each time is more evident that the psychological, social and physical effects of this condition do not decrease with the age. Acne and some of its treatments may lead to depression and other psychiatric problems that, if not properly diagnosed, could have serious consequences [1-3]. Previous studies have examined the relationship between having acne and various psychological factors [4]. The measurement focus shifted from psychological correlates (eg, personality) and emotional triggers (eg, stress) to measuring the effect of acne on patients' quality of life. Skindex [4] is a validated 29-item instrument to measure the effects of skin disease on patients' quality of life. Results are reported as 3 scale scores (functioning, emotions, and symptoms) and a composite score (average scale score). In addition, dermatologists rated the clinical severity of patients' skin disease, and patients responded to a global question about how they are bothered by acne. Higher Skindex scores indicate greater effects on quality of life. Second, in a multivariate analysis, older adults with acne *vulgaris* reported significantly greater overall effects on their quality of life than did younger patients, even when controlling for the clinical severity of the acne. Finally, this study confirmed other research suggesting that more severe acne is more likely to be associated with psychological factors such as anxiety, and with greater effects on patients' lives. However, there are other factors that contribute to the effects of acne on patients' quality of life, including patient age. In fact, in a previous study, the psychosocial effects of acne on quality of life were found to be influenced more by patients' self-perception of their acne severity than by the objective severity of the disease [4].

Acne in the adult becomes a drawn out problem and with lasting effects. With aging, the skin loses collagen and more likely the physical scars could be permanent. Furthermore [3], the acne in women who are pregnant or breast-feeding, is a major challenge to the level of therapy, given the impossibility of their inclusion in clinical trials.

PREVALENCE

Most acne cases are said to occur during adolescence and spontaneously resolved in adulthood; therefore epidemiological studies have mainly focused on acne in adolescents. However, there has been a remarkable increase in the number of these studies in adults; even if the results are not always consistent. For example, an epidemiological study reported 4597 cases of acne (16%) among 28714 patients examined in five dermatology clinics in France [5]. The average age of patients corresponded to 24 years old and 66% were male. A study performed in Boston in 20749 patients aged from 15 to 44 years old concluded that 27% of women and 34% of men had acne. In another study with 200 patients aged over 25 years old and who had mild to moderate acne, 76% were female and 24% male. According to this study, acne in the adult is defined as the acne that emerges from 25 years old, occurring in 18.4% of women and 8.3% of men. In another study in 2000 healthy men and women aged 18-70 years old, it was observed that the first 16 years old, acne is more prevalent in men and that after 23 years old, becomes more prevalent in women. In a sample of 300 women, it was determined that 70% had clinically evident acne according to the results of questionnaires (WHO-5). Another survey established a prevalence of 42% of women with acne aged 26-45 years old. A more recent study confirmed that the prevalence of acne in adult women is high with more than 41% of acne. However, only about 22% looked for medical treatment [5]. It was also observed that the acne in adult occurred mainly in sensitive and slightly seborrheic skin, which is quite important to decide about the type of treatment to use [5].

PHYSIOPATHOLOGY

Acne *vulgaris* is a pathological dysfunction in the sebaceous follicles with multifactorial etiology. The acne etiology is not very well clarified, but it has been accepted that its

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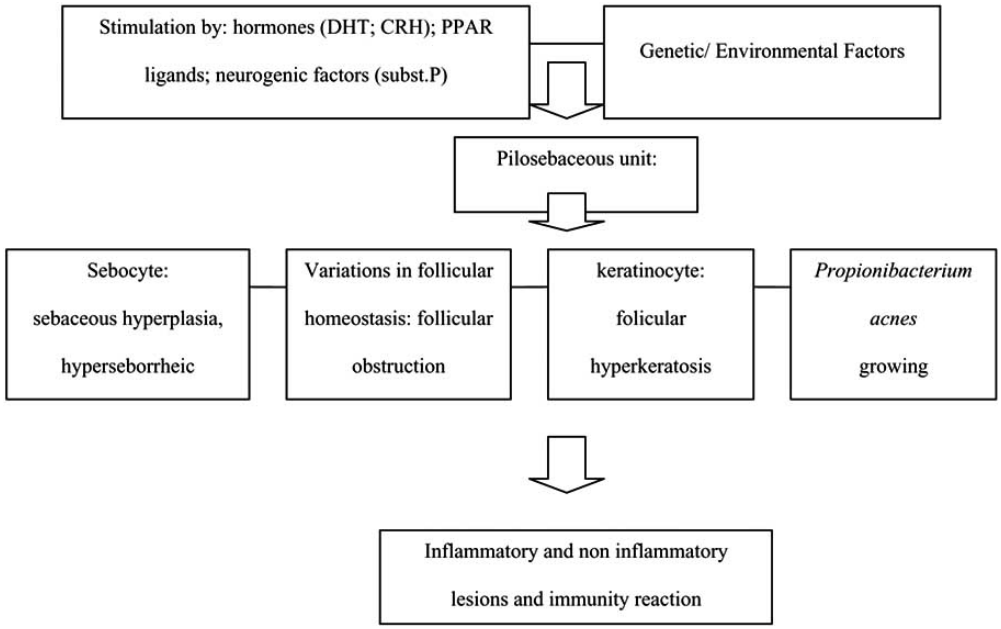


Fig. **(1).** Algorithm of acne etiology (adapted from Krautheim [7]).

pathogenesis is multifactorial, with abnormal follicular differentiation and increased cornification, abnormal activity of the sebaceous gland and bacterial hyper-colonization, as well as inflammation and immunologic reaction (Fig. (**1**)) [6].

Probably acne *vulgaris* is an authentic inflammatory disease, and the androgeneous hormones, PPAR (peroximal proliferators activated receptor), neuropeptides and environment factors are able to interrupt the natural cycle of the sebaceous follicles and form the micro-comedones. Pro-inflammatory lipids and cytokines seem to act as mediators for the beginning of the acne lesions. *Propionibacterium acnes* (*P. acnes*), a Gram positive microaerophile bacteria is responsible for the local inflammatory response of acne, with the activation of monocytes and production of cytokines. The inflammatory lesions may include: papules, pustules and cystic nodules. It is believed that greater sensitivity to *P. acnes* and their metabolites might be related to the severity of acne [6].

There are no changes in the composition of sebum in hyperseborrheic skin, predominantly free fatty acids, resulting from the degradation of triglycerides. This change may contribute to hyperkeratinization by increasing cell adhesion. The hyperkeratinization, with consequent follicular obstruction results in the formation of non-inflammatory lesions (Fig. (**2**)): comedones, initially closed – "white spots", and, months later, opened "black spots" [8].

Although the causes of acne are not completely clarified, it seems that one of the main causes is the hormonal origin, both in adolescences and adults [9]. The major hormones involved in the etiology of acne are androgens, taking into account that 5 α-reductase type 1, responsible for the conversion of testosterone into dehydrotestosterone (DHT), appears to be most prevalent in the sebaceous glands of isolated acne areas and to have greater activity in women with moderate to severe acne. Concerning to suprarenal androgens, the serum androsterone glucuronide is increased in women adult, and the testosterone and dehydroepiandrosterone sulphate (DHEAS) are within the normal values. Other hormones such as corticotrophin-releasing hormone (CRH) and melanocytes stimulating hormone (MSH) express their receptors

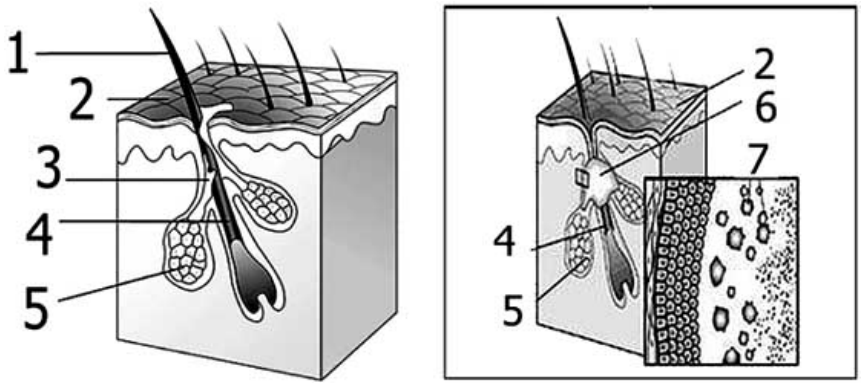


Fig. **(2).** Internal structure of the skin (normal and with acne inflammation).

1- Hair; 2- Skin Surface; 3- Sebum; 4- Follicle; 5- Sebaceous Gland; 6- Blockage of Follicle opening; 7- Bacteria. (Adapted from http://www.herbalremedies.com/acne.html)

on the sebaceous glands. While MSH is related to the inflammatory process, CRH may be considered a hormone that promotes lipogenesis in sebocytes (testosterone and growth hormone induce the negative feed back of CRH). Thus, research suggests that CRH is involved in the clinical development of acne, androgenetic alopecia, skin aging, xerosis and other skin disorders associated with variations in the production of lipid sebum [8, 10].

To examine the influence of neurogenic factors in the pathogenesis of acne, were evaluated quantitatively the effects of neuropeptides in the morphology of the sebaceous glands *in vitro* using the electron microscopy. It was found that substance P promoted the proliferation and differentiation of the sebaceous glands [11].

Genetic and environmental factors are other external factors mentioned, even though empirically, in the pathogenesis of acne. Regarding inheritance, there is some evidence based on studies of twins that suggests that acne may have a hereditary component [12].

According to Christos Zouboulis [13] (from the dermatology department of the Medicine University in Berlin), the current research is modifying the classic vision of acne pathogenesis through the identification of the upstream mechanisms. A causal linking between stress and emotional acne has been claimed during a long time. There are some evidences that the underlying molecular mechanism is related to the expression of the neuro-endocrine mediators' receptors by the sebaceous gland. Recent studies have indicated that the human sebocytes express functional receptors for hormonal release of corticotrophin, melanocortin, vasoactive intestinal polypeptide, β-endorphin, neuropeptide Y, among others. After ligand connection, these receptors modulate the production of the cytokines inflammatory metabolism, the proliferation, the differentiation, the lipogenesis and the androgeneous metabolism in sebocytes, as mentioned before. These neuro-endocrin factors seem to mediate stress systemically and topically, stimulating the sebaceous gland, affecting finally the clinical manifestation of acne [13].

This new concept of acne pathogenesis will certainly lead to the introduction of new drugs for the acne treatment, especially those whose action includes the inhibition of the main inflammatory mechanisms involved.

DIAGNOSIS AND ESTABLISHMENT OF GRADING CRITERIA FOR ACNE SEVERITY

The basic morphology of acne and the variation in the number of acne lesions over time does not permit an assessment and a simple diagnosis purpose of this pathology. There have been developed various measurements based on clinical examinations and photographic documentation.

Historically, the measurements of acne are divided into two groups: the lesions countdown and the graduation. Graduation is an estimation of the degree of severity which is quite subjective. It is based on observations of dominant lesions, evaluating the presence or absence of inflammation. Sometimes it is problematic because many variables are involved. Some graduators (technical specialists) use reference scales based on photographs. This method has several limitations: lack of palpation; small comedones and inflammatory lesions are generally not viewed; residual erythema, changes in pigmentation or excoriations are minimized. However, the polarized light and fluorescence photography can partly improve this assessment [14]. A study was designed with the objective to achieve a reliable method of lesions counting based on a facial diagram divided into five segments. It was concluded that the reliability of the method is acceptable if it is implemented by the same technician. The variability between these technical specialists seems to be reduced through a standardized training. The papules are the easiest lesions to assess, perhaps because they are more visible, especially in Caucasian patients, besides that the number of papules is usually lower than the number of comedones [15].

In 1997, Doshi *et al.* developed a comprehensive system of acne graduation [14]. This system divides the face, chest and back in six areas (forehead, cheeks, nose, chin; bust and back) and assigns a factor 1, 2 or 3 to each area in accordance with the extension. To each type of lesion is assigned a value depending on the severity: absence of lesions = 0; comedones = 1; papules = 2; pustules = 3; nodules = 4. The scores for each area results from the scores of lesions more severe multiplied by the relevant factor. The final sum total score is classified as: slight (1-18), moderate (19-30), severe (31-38); very severe (> 39). A very similar system has been proposed by Dreno *et al*. [16] in 1999. Recently Rizova and Kligman [14] used the photography with parallel polarized light and cross in combination with video microscopy and measurement of the production of the sebum.

Concerning differential diagnosis, there are two diseases that are rather frequently confused with acne: the rosacea (often called acne rosacea in the older literature), the perioral dermatitis and the malassezia folliculitis. Rosacea may be distinguished from acne by several features, such as: age (rosacea patients are generally older than are acne patients, except in acne in the adult), type of lesion (acne lesions are follicular, while rosacea lesions are not) and distribution pattern (rosacea usually affects primarily the central third of the face, while acne is generally more widespread on the face, neck, back, and chest). Table **1** summarizes the referral guidelines for acne and rosacea [17].

Perioral dermatitis is a difficult disorder to define because of variable clinical presentations. Its distribution pattern is generally perioral, although occasionally it may be more widely distributed on the face. This disorder is seen most commonly in young adult women, but may affect both genders and all ages. Clinically, it is characterized by a combination of eczematous and acneiform features. When eczematous features are absent, it may be difficult to differentiate from acne, with the perioral pattern often the most useful clue [17]. Malassezia folliculitis (previously called 'pityrosporum folliculitis') is due to proliferation of a yeast, called *malassezia*, within the hair follicles. It presents as an itchy, acne-like eruption and most often affects the trunk and it can also cause pityriasis versicolor and seborrhoeic dermatitis [18]. Some adolescents with recalcitrant follicular pustules or papules may have acne and malassezia folliculitis simultaneously. According to Zargari [20], the malassezia *folliculitis* can be differentiate from acne *vulgaris* in some aspects: 1) malassezia *folliculitis* is pruritic, especially after

Table 1. Referral Guidelines for Acne and Rosacea

Acne
Acne that has not responded to appropriate therapy
Candidates for isotretinoin
Rarer variants of acne (acne excoriée, chloracne, acne fulminans)
Suspected Demodex folliculitis, Pityrosporum folliculitis
Female patients with suspected endocrine disorder
Pregnant patients with acne
Patients with acne scarring
Rosacea
Rosacea that has not responded to appropriate therapy
Candidates for isotretinoin
Candidates for electrosurgery, laser surgery, or dermabrasion for the treatment of telangiectasia or phymatous changes
Patients with ocular rosacea (dermatologist and ophthalmologist referral)

sweating; 2) trunk involvement and sparing of the face are among the other features of malassezia; 3) antibiotics have no role in treating malassezia [19, 20].

TYPES OF ACNE

According to age criteria, acne can be classified as neonatal acne, infant acne, puberty acne and acne in the adult [5].

Different types of acne exist with several severity degrees that could characterize the acne in the adult (Table **2**) [5, 21-23].

Table 2. Types of Acne and its Characterization

Type of Acne	**Characterization**
Acne *vulgaris*	common type of acne with presence of black spots, white spots, papules and/or pustules
Acne conglobata/nodular	very severe type of acne with presence of some nodules and cutaneous injuries
Acne papulopustular	type of acne characterized by the presence of pustules and papules
Acne excorie	type of acne characterized by the presence of scratched or picked pimples. It is more common in females than males, and can be a sign of stress or depression
Acne mechanics	type of acne that is originated by the reaction to a constant pressure on the skin, friction, heat or when the skin is always covered
Chloroacne	cutaneous rash characterized by many comedones due to the exposition of chlorinated or chemical herbicides agents
Acne steroid	acne that appears after a long exposition to the corticosteroids

Generally, the adult acne is characterized by presenting a more inflammatory component with fewer comedones and lesions tend to allocate more at the bottom of the face [5].

TREATMENT

Currently, there is a huge variety of topical and systemic drugs for the acne treatment (Table **3**) [24]. The topical treatment is indicated for mild to moderate acne as adjunctive treatment of inflammatory and nodulocystic acne. The drugs can be absorbed through the transdermal or transfollicular route, which will depend on the solubility, polarity and the particles size in the formulation. Particles with sizes between 3-10 μm can penetrate into the follicular ducts, while larger particles are retained on the skin surface and smaller particles are distributed by the stratum corneum and hair follicle [8, 25].

Table 3. Acne Treatments and the Physiopathologic Factors and Acne Type Associated (adapted from Fernandes & Rodrigues [8]; Usatine *et al.* [24])

Acne Physiopathologic Factors	**Treatment**
Hyperkeratinization	Tazaroten; tretinoin; adapalen; azelaic acid; salicilic acid; oral isotretinoin
Hyperseborrhea	Anti-androgens (women); topical/ systemic retinoids
Bacterial proliferation	Benzoyl peroxide; antibiotics; tazaroten; tretinoin; adapalen; azelaic acid; oral isotretinoin
Inflammation	Intralesional corticosteroid; antibiotics; azelaic acid; benzoyl peroxide
Hormonal disregulation	Oral contraceptives; anti-androgens; spironolactone
Acne Type	**Treatment**
Comedogenic	Tazaroten; tretinoin; adapalen; azelaic acid; benzoyl peroxide
Light Papulopustular	Antibiotics and benzoyl peroxide; tazaroten; tretinoin; adapalen; azelaic acid
Moderated Inflammatory (papulopustular or nodulocystic)	Begin with antibiotics and benzoyl peroxide; Addition of: tazaroten; tretinoin or adapalen if the inflammation increases
Severe cystic	Isotretinoin

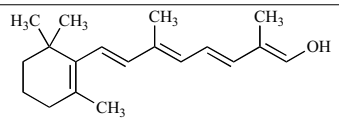
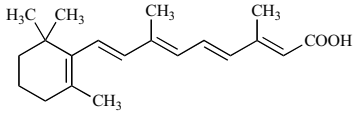
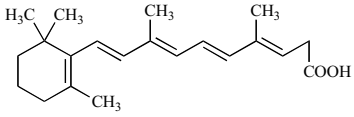
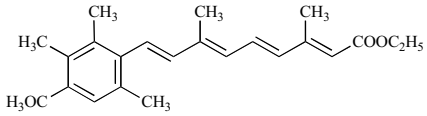
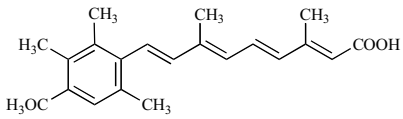
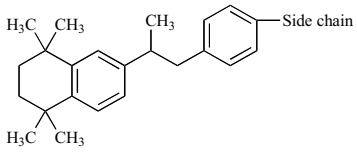
The hydroalcoholic solutions and gels are those that generally cause a more efficient drug release in topical formulations [3]. The systemic treatment is indicated in cases of moderate to severe acne, especially when the acne scars start to appear. The antibiotics with anti-inflammatory properties, such as tetracyclines and macrolides are the therapeutic choice for papulopustular acne, even if there is some bacterial resistance. Isotretinoin is the best therapeutic treatment

for papulopustular acne, severe acne and nodulocystic / conglobata acne. The hormonal treatment with anti-androgeneous properties represents an alternative regimen for women. Corticosteroids in reduced dose (prednisone, prednisolone or dexametasone) are indicated in patients with acne or adrenal hyper-androgenism. The future trends of long term treatment represent regimens of low dose isotretinoin, new formulations of isotretinoin (micronised isotretinoin as solid lipid nanoparticles (SLN), complexed with cyclodextrins (CDs), isotretinoin metabolites, combined treatments to reduce toxicity and act on more pathological factors, sensibilising-insulin agents, type 1 inhibitors of the 5 α-reductase, new molecules of antisense oligonucleotides, and anti-inflammatory agents, such as lipoxigenase inhibitors [26, 27].

TOPICAL THERAPY

Topical retinoids are derived from vitamin A and are classified in three groups: non aromatics - tretinoin and isotretinoin; monoaromatics and polyaromatics - adapalen and tazaroten. Other classification is the first, second and third generation retinoids (Table **4**).

Table 4. Retinoids Molecular Structure

FIRST GENERATION	
RETINOL	
TRETINOIN	
ISOTRETINOIN	
SECOND GENERATION	
ETRETINATE	
ACITRETIN	
THIRD GENERATION	
AROTINOL	

The retinoic acid receptors are α, β and γ -RAR and RXR receptors and the citosolic skin binding proteins are the CRABP, which lead to an anti inflammatory and comedolytic action. Retinoids are considered the first line treatment for acne, being also a maintenance therapy. These drugs cause the desobstruction of the pores, preventing the formation of white spots and still present the benefit of decreasing the first signals of cutaneous aging, being therefore an essential treatment for acne in the adult. However, it can irritate the skin and provoke sensitization to the solar exposition. Therefore it is important to use daily solar protection. According to a recent study, the retinoic acid/ β-CD complex shows a significant increase of the effectiveness and tolerance to the acne *vulgaris* treatment, which will also increase the patients' compliance to this treatment [28].

On the other hand, it is usual the topical antibiotic combination with retinoids to treat comedogenesis, bacterial growth and inflammation. This combination also increases the effectiveness and tolerance to the treatment. On the other way, benzoyl peroxide can be used in combination with topical retinoids to reduce the dose of antibiotic.

The transdermal penetration and systemic bioavailability of topical retinoids are not yet completely clarified. Thus, there is not a consensual opinion about the use of topical retinoids during the pregnancy [29].

The main topical retinoids are:

- Adapalen: one of the most topical retinoids used (Fig. (**3**)) that is commercially available as 0.1% gel, cream or solution form. In a randomized study with 268 patients with facial acne *vulgaris*, it was found that the 0.1% gel was as effective as the 0.025% tretinoin gel. Another study in the USA showed that the group of patients treated with adapalen showed a greater reduction in inflammatory and non-inflammatory lesions of acne, as well as the side effects compared with the group treated with tretinoin [3, 30]. However, a comparison study between 0.1% tretinoin microspheres gel, 0.05% tretinoin gel and 0.1% adapalen gel, has shown that tretinoin was more effective [31, 32]. Thus, it appears important to consider the drug dosage form and the type of formulation in comparative studies between different drugs.

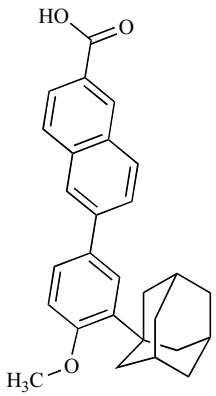


Fig. **(3).** Adapalene molecular structure: IUPAC NAME: 6-[3-(1-adamantyl)-4-methoxyphenyl]naphthalene-2-carboxylic acid).

- Tazaroten: introduced in 1997, tazaroten is one of the most recent topical retinoids for the treatment of acne. It is a synthetic acetilenic molecule which is rapidly con-

verted by esterases in its active metabolite, tazarotenic acid in keratinocytes (Fig. (**4**)). The tazarotenic acid has the ability to bind and activate the nuclear retinoic acid receptors. The 0.05% and 0.1% concentrations are available in cream and gel formulations. Tazaroten is also indicated for the treatment of plaque psoriasis and photoaging. Tazaroten is the most irritant topical retinoid. It can not be used during pregnancy because it caused birth anomalies in animals' studies. In a study in which a 0.1 % tazaroten gel was compared to 0.025% tretinoin gel, the first one has shown to be more effective in reducing non inflammatory lesions and equally effective in reducing inflammatory lesions [3,33]. In another study comparing the 0.1% tazaroten gel and 0.1% tretinoin microsponge gel, the tazaroten again showed greater efficacy. Regarding the comparison between a 0.1% tazaroten cream and a 0.1% adapalen cream, a randomized double-blind trial showed that the tazaroten cream had greater efficacy and tolerability. Tazaroten is currently used as an alternative treatment to tretinoin and adapalen in refractory cases [34, 35].

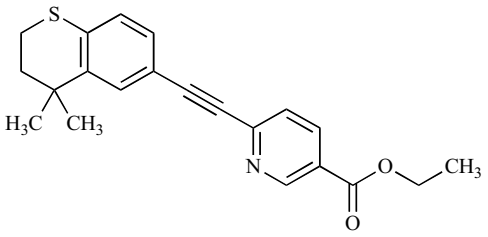


Fig. **(4).** Tazarotene molecular structure: IUPAC NAME: ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]pyridine-3-carboxylate.

- Tretinoin: Corresponds to the trans-retinoic acid form. The formulations include 0.025- 0.1% topical creams and 0.01-0.025% gels. However, there has been emerging new sustaining release systems in which the active substance is vehiculated in microsponges or polymers in order to remain at the stratum corneum and thus promote comedolisis and modulation of the keratinocytes proliferation. The collateral effects include redness, descamation, dryness, and burning tingle [3].

The tretinoin complexation with 2,6-dimethyl-beta-cyclodextrin (DM-β-CD) will enhance the drug release by promoting skin permeation and alleviation of drug induced local irritation. It will also overcome its low solubility in water and low stability. According to Ascenso & Cabral Marques (poster presented at the Congresso Nacional de Ciências Dermatocosméticas, 2007): the obtained complex is soluble (A_L phase solubility diagram corresponding to 1:1 stoichiometry), the time for maxim complexation goes on for 8 days and the complexation constant is quite high, which suggests that the complex formed is stable. This study based on various analytical techniques including differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR), X-ray diffraction and molecular modelling demonstrated that it is possible to complex tretinoin with DM-β-CD, leading to new perspectives in anti-acne formulations for topical application (Fig. (**5**)) [36].

Fig. **(5).** Tretinoin/ DM-β-CD complex: stable form and the instable form The most stable complex has -5723.4322023 Hartrees (Hartree ≈ 2625.5 kJ/mol) *(*Molecular Modelling Software: Gaussian 03 Program).

- Isotretinoin: exists in 0.05-0.1% cream and 0.05% gel form. In a double-blind trial with 268 patients, to whom was applied 0.05% isotretinoin gel twice daily for 14 weeks. It was observed the effectiveness of this drug for the treatment of mild to moderate acne, reducing both inflammatory and non-inflammatory lesions. The drug was well tolerated; with withdraw of only two patients because of skin irritation. Side effects are similar to those of tretinoin [3, 37].

There are other topical retinoids used in the treatment of acne, such as the retinaldehyds and β-glucuronide retinol.

Topical antibiotics have demonstrated they have not only bactericidal action, but they also have an anti-inflammatory action through the inhibition of leucocitary chimiotaxy and lipase production by *P. acnes* [38].

- Sodium Sulfacetamide: a topical antibiotic that inhibits P. acnes and opens the obstructed pores, being efficient for the treatment of the inflammatory acne. There is in 10% topical formulations combined with 5% sulphur.
- Clindamicine: topical gel, lotion or 1% solution proved to be safe and well tolerated. The possible collateral effects are dryness and skin irritation. The possible occurrence of pseudomembranous colitis is not clinically relevant [7].
- Eritromicine: available in 1-4% solution, lotion and gel form reduces significantly the P.acnes and Micrococcaceae in the sebaceous glands ducts.

Several combinations of drugs with therapeutic benefits have been already demonstrated: 3% erythromycin and 5% benzoyl peroxide gel; 4% erythromycin and 0.025% tretinoin gel; 2% erythromycin and 0.5% isotretinoin gel; 1.2% erythromycin and 0.377% zinc acetate solution; 1% clindamycin and 5% peroxide benzoyl gel; 1% clindamycin phosphate and 0.025% tretinoin gel [3, 7, 39, 40].

A comparison study between the combination of clindamycin / benzoyl peroxide and clindamycin / tretinoin demonstrated that the first combination is more effective in the treatment of acne *vulgaris*. A similar result was observed in another comparative study between the combination of erythromycin / benzoyl peroxide, and erythromycin / treti-

noin. The benzoyl peroxide contributes to decrease the resistance [40, 41].

Benzoyl peroxide in systemic and topical dosage forms reduces the propagation of *P. acnes* and removes the dead cells of the skin, preventing comedones. It is believed that the action mechanism corresponds to the degradation of bacterial proteins by the release of free radicals of oxygen. Benzoyl peroxide exists in 2.5-10% lotions, creams, gels and cleaning products. The main collateral effect is the extreme dryness of the skin. When compared with antibiotics, it is observed that 5% benzoyl peroxide is at least as effective as formulations of clindamycin and erythromycin. Then this is a useful adjuvant therapy [3].

Azelaic acid is a saturated dicarboxylic acid found naturally in wheat, rye, and barley (Fig. (**6**)). It is a natural substance that is produced by Malassezia furfur, a yeast that lives on normal skin. It is effective against a number of skin conditions, such as mild to moderate acne, when applied topically in a cream formulation of 20%. The drug target is 3-oxo-5-alpha-steroid 4-dehydrogenase 2 which converts testosterone (T) into 5-alpha-dihydrotestosterone (DHT) and progesterone or corticosterone into their corresponding 5-alpha-3-oxosteroids. It plays a central role in sexual differentiation and androgen physiology. It works in part by stopping the growth of skin bacteria that cause acne, and by keeping skin pores clear. Azelaic acid's antimicrobial action may be attributable to inhibition of microbial cellular protein synthesis. It also proved to be efficient for the treatment of the dark spots that can appear in black patients with acne. Azelaic acid is well tolerated by almost everybody and can be safely used during years.

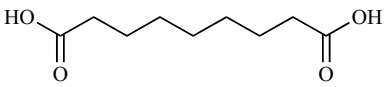


Fig. **(6).** Azelaic Acid: nonanedioic acid.

The collateral effect may include skin dryness and a certain lack of pigmentation. A comparison study between the combination of azelaic acid cream / oral minocycline and oral isotretinoin in the treatment of severe acne allowed to conclude that the combination, although not as effective, it is better tolerated by patients [42].

SYSTEMIC THERAPY

Isotretinoin is a potent oral retinoid that is reserved for the treatment of cystic and severe acne. It is still the only available treatment that acts in four acne physiopathologic factors and therefore the oral isotretinoin is the standard treatment for severe acne. Isotretinoin has produced an 80% reduction in sebum excretion, comedogenesis, and ductal and surface *P. acnes* within 4 to 8 weeks of use and demonstrated anti-inflammatory activity [2]. Therapy should be started on day 2 or 3 of the menstrual cycle. Therapeutic dose is 0.5-1.0 mg/kg per day and treatment duration is usually 20 weeks. Improvement may continue for up to 5 months after ending therapy. Relapse can occur in 15% of patients, particularly in younger ones. However, isotretinoin is a theratogenic drug. Other adverse effects of isotretinoin include anemia and/or thrombocytopenia, pruritis, exuberant granulation tissue, cheilitis, epistaxis, dry skin, ocular and vaginal dryness, arthralgia, secondary skin infection with *S. aureus*, depression, and, rarely, pseudotumor cerebri and skeletal hyperostoses. Occasionally, patients may have mildly to moderately raised liver function test results. Some of the adverse effects are treatable: dryness and irritation are treatable with emollients, while pain or stiffness of the bones and joints can be controlled with aspirin or nonsteriodal anti-inflammatory drugs. Hypertriglyceridemia is usually mild and can be controlled by dietary management and weight control. Elevations of serum triglycerides or liver enzymes may occur, but are not usually clinically significant. Baseline liver function tests and fasting lipid profile are suggested, with recommendations for follow-up monitoring ranging from every 4 to 8 weeks to less frequently if baseline values are normal [2].

Oral antibiotics are generally prescribed for six months or less. However, the *P. acnes* can become resistant to antibiotics. It is quite important to take into account the recommendations about antibiotics: the choice of the antibiotic type, therapeutic dosage; combination of drugs, duration of treatment and therapy for maintenance [43].

- Erythromycin: is effective against a broad spectrum of bacteria, including P. acnes. The most common side effect is gastrointestinal irritation.
- Tetracycline and derivatives: reduce the papules and pustules (inflammatory lesions) of acne. It should not be taken by women who are pregnant or breast-feeding because it may affect the development of children bones and teeth. The most common synthetic derivatives are minocycline and doxycycline. Minocycline presents fewer cases of bacterial resistance and doxycycline is effective in inflammatory acne.
- Limociclin: in 300-600 mg dosages. A comparative study between limociclin and minoclin for the treatment of inflammatory acne concluded that limociclin showed greater efficacy [44, 45].
- Oral contraceptives can be used as a good treatment for many teenage and adult women. The therapy consists on blocking the production of ovaric and adrenal androgeneous hormones that control the sebum production in the skin. The hormonal therapy is an option of treatment for women with acne when the conventional treatment fails. Comparative studies of contraceptive therapy indicated that the most effective treatment is still the combination of ethinylestradiol 0.035 mg with 2 mg cyproterone acetate [46].

Spironolactone, an androgen receptor blocker, is used in the treatment of hirsutism and acne in women (Fig. (**7**)). In published studies, it was determined that the range of effective dose was 100-200 mg / day. However, at this range the majority of patients (91%) had side effects dependent on the dose: menstrual irregularities; central nervous system symptoms; hyperkalemia; slight reduction in blood pressure. A retrospective study was performed on 85 women who took 50-100 mg of spironolactone therapy with and without reference treatment for acne. Despite some limitations of this study, spironolactone was effective and well tolerated in low doses [47].

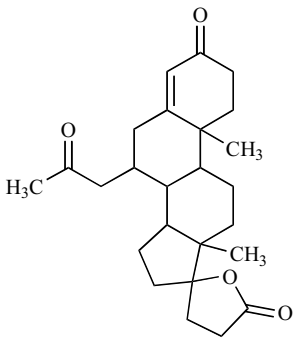


Fig. (7). Spirinolactone IUPAC NAME: S-[(7R,8R,9S,10R,13S, 14S,17R)-10,13-dimethyl-3,5'-dioxospiro[2,6,7,8,9,11,12,14,15,16-decahydro-1H cyclopenta[a]phenanthrene-17,2'-oxolane]-7-yl] ethanethioate.

Flutamide and other similar compounds, nilutamide and bicalutamide are non steroidal anti-androgens (Fig. (**8**)). Buserelin and similar compounds, goserelin, nafarelin, gonadorelin and leuprolide are analogues of luteinizing hormone-releasing hormone (LH-RH) and have proven its effectiveness in the treatment for acne [48]. The flutamide's main indication is the treatment of hirsutism, as 250 mg the therapeutic dose is. It must be administered concurrently a contraceptive device due to its theratogenic effect. After oral administration, flutamide is converted into a potent metabolite, a 2-hydroxy-flutamide. A study was performed to compare the relative effectiveness of two new anti-androgens (flutamide and finasteride) with ciproterone acetate (CPA) in low and high doses in the treatment for moderate to severe acne in hyperandrogenic women. The low and high doses of CPA with ethinylestradiol were equally effective and comparable to the effects of a reduced dose of flutamide. Finasteride was less beneficial [49]. However, there are still few studies that prove the effectiveness of spironolactone and flutamide as therapeutic agents for acne.

In relation to various drug interactions, Akhavan & Bershad [3] refer the main interactions with the drugs used in the treatment for acne.

According to recommendations of the International Consensus on Acne, the reference therapy is the combination of retinoids and antibiotics [50].

According to Galderma investigators, the most adopted evaluation method in the previous major clinical studies of various anti-acne agents is based on the level of effectiveness and tolerability of such agents. Two other parameters that should be considered are the acne recurrence after treatment and whether there is any risk of developing bacterial resistance to antibiotics.

Finally, there are other procedures for the acne treatment, such as: chemical peelings, dermabrasion, skin cleaning, draining and surgical extraction (of comedones, cysts, etc.), collagen injection (shallow scars are elevated by collagen injections), intralesional injection with corticoids (injected directly into inflamed cysts) and phototherapy (laser rays at 1450 nm) [51].

A study has shown that the salicylic acid peelings are effective and safe for the therapy of acne *vulgaris* in Asian patients. Both inflammatory and noninflammatory acne lesion counts were decreased in proportion to the duration of treatment. Dr. Cunliffe's acne grade was statistically significantly decreased after treatment. The side effects were tolerable in most cases, and all patients were pleased with their peel results. Stratum corneum hydration, skin surface lipid, skin pH, and transepidermal water loss were unchanged from baseline levels [52]. Glycolic acid is also used in chemical peelings and is applied to peel off the top layer of skin to reduce scarring.

To evaluate the efficacy and tolerability of methyl aminolevulinate with photodynamic therapy (MAL-PDT), a randomized study was performed in patients with facial moderate to severe acne *vulgaris*. Efficacy evaluation included changes from baseline in numbers of noninflammatory and inflammatory lesions, changes from baseline in global acne severity grade and clinical assessments of clinical improvement by patient and evaluating dermatologist. Pain scores during treatment and local adverse effects were also evaluated. Twelve weeks after treatment the treatment group showed 68% reduction from baseline in inflammatory lesions but no reduction in number of noninflammatory lesions after treatment. All patients experienced moderate to severe pain during treatment and developed severe erythema, pustular eruptions and epithelial exfoliation. It was concluded that MAL-PDT is an effective treatment, but very painful and it should still be made efforts to optimize this therapy [53].

Recently radiation with variable wavelength (peaks 415 and 660 nm) has been used. These radiations cause the photoexcitation of porphyrins produced by *P. acnes*, production of oxygen and subsequent bacterial destruction.

These techniques are sufficiently useful in the case of acne in the adult, mainly because help to eliminate also the lesions of the skin [2, 24].

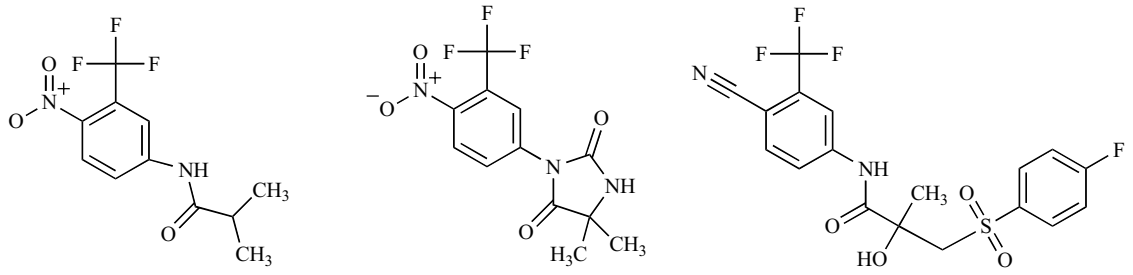


Fig. (8). Non steroidal anti-androgens: Flutamide, nilutamide, bicalutamide.

Concerning the "natural products" used in traditional medicine for the treatment of acne, these products are constituted by plant extracts as Propolis, Echinacea Angustifolia, Aloe Vera, Tabebuia Avellanedae, Burdock root, Chaparral, Yellow Dock Root, Red Clover, Dandelion, Lavender, Strawberry (leaves), Turmeric, Horsetail, Angélica, Gotakola [54]. The value of such treatments is generally unknown, because its effectiveness is rarely tested in clinical trials.

At least there are also some daily and simple habits that can help to prevent adult acne, like avoiding oily makeup (the use of only "noncomedogenic" products); washing gently; keeping hair sprays and gels away from the skin; avoiding stress and having a healthy diet rich in fruits and vegetables which will contribute to healthy, glowing skin [51].

CONCLUSION

The world-wide acne treatments cost represents about 12.6% of the annual costs of all the treatments on skin diseases. In this way, the importance of the adult acne treatment should be highlighted, considering a long lasting problem, of complex causes and originating, many times, symptoms of depression and anxiety that can become more serious than in adolescence. Its negative effect on the emotional well-being and the social function is frequently higher than in other diseases, for example, asthma or epilepsy. Significant progress in the acne studies has been observed. However, there are some fields to be exploited such as the main cause of the acne severity and the design of more specific, effective and safe drugs. Understanding the pathophysiology of acne will facilitate the development of more effective acne therapies. Ideally these drugs should be also indicated for aging. Another approach could be the design of new drug delivery devices.

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