



DRUGS USED IN TREATMENT OF ACNE

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ABSTRACT

Acne Vulgaris is one of the most common skin disorders which dermatologists have to treat. It mainly affect adolescent, though may present at any age. In recent years, due to better understanding of the pathogenesis of acne, new therapeutic modalities and various permutation and combinations have been designed. In topical agents; benzoyl peroxide, antibiotics, retinoids, et care the mainstay of treatment; can be given in combinations. While systemic therapy includes oral antibiotics, hormonal therapy, and isotretinoin, depending upon the need of patients it has to be selected. Physical treatment in the form of lesion removal, photo-therapy is also helpful in few of them. Since various old and new topical and systemic agents are available to treat acne, it some-time confuse treating dermatologist. To overcome this, panel of physicians and researchers worked together as a global alliance and task force to improve outcomes in acne treatment. They have tried to give consensus recommendation for the treatment of acne. Successful management of acne needs careful selection of anti-acne agents according to clinical presentation and individual patient needs.

KEYWORDS: Acne, Treatment, Consensus recommendation.

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease that affects the hair follicle and sebaceous glands. Acne vulgaris mostly appears in adolescence under the effect of dehydroepiandrosterone (DHEA) and may persist through the early thirties. Propionibacterium acnes which were recently renamed Cutibacterium acnes is the main organism involved in the pathogenicity of acne vulgaris. Acne vulgaris is common in adolescents and ranks number eight in the list of the most prevalent diseases worldwide. It can present with inflammatory lesions like comedones or non-inflammatory lesions, and is mainly found on the face and also occur on the shoulder, trunk, and back.^[1-5] There are four key elements in acne pathogenesis, follicle colonization with Propionibacterium acnes (P. acnes), hyper-keratinization, alteration of amount and quality of sebum, and inflammatory reaction^[6] Acne's negative emotional and psychological impact is generally significant and persistent, including depression and anxiety.^[7] Acne is more common in males. It is estimated that around 20% of the population may have severe acne, which will result in scarring. Acne can also occur in newborns, although the majority of cases cure spontaneously.^[5] There are a variety of factors that might contribute to acne exacerbation, for instance, the use of medicines such as steroids, excessive exposure to sunlight, endocrine problems such as Polycystic ovarian syndrome (PCOS), pregnancy, and genetic variables that influence

the quantity of branched fatty acids in sebum are all factors that might contribute to acne.^[8] Acne occurs due to the sebaceous gland hypersensitivity to an average circulating level of androgen hormone, aggravated by Cutibacterium acnes and inflammation. During puberty and under the influence of androgens, the production of sebum increases as 5-alpha reductase converts testosterone into the more active form dihydrotestosterone (DHT), which binds to specific receptors in the sebaceous glands, causing an increase in sebum production and hyperproliferation of the sebaceous epidermis (follicular epidermis hyperproliferation), resulting in sebum retention. Distended follicles with sebum break and release pro-inflammatory mediators into the dermis, causing inflammation. P. acnes, Staphylococcus epidermis, and Malassezia furfur are the most common bacteria that induce inflammation and follicular epidermis hyperproliferation in the skin.^[9,10] Acne vulgaris is clinically diagnosed. However, women of reproductive age should be asked whether they have a history of hirsutism or dysmenorrhea. If the test results are positive, then testosterone, LH, FSH, and Dehydroepiandrosterone (DHEA) levels should be tested.^[11] The cornerstone of acne management has remained substantially unaltered over the last decade but in conjunction with increasing bacterial resistance to antibiotics throughout the world. Topical and oral antibiotic monotherapy is being phased out in favor of more limited usage across the world.^[12]

It's important to remember that acute therapy and long-term maintenance medication in the same patient with acne vulgaris might have a little resemblance, especially if the acne is moderate to severe. The purpose of acute therapy is to improve the patient's condition as quickly as possible; this usually necessitates a combination of drugs, including oral antibiotics, with other medicine. For patients with mild to moderate acne, topical medications are considered as main treatments.^[13]

Topical therapy: Topical therapy is useful in mild and moderate acne, as monotherapy, in combination and also as maintenance therapy.

A. Benzoyl peroxide

It is an effective topical agent since many years and is available in different formulations (washes, lotions, creams, and gels) and concentrations (2.5–10%). The stability is very dependent on its vehicle. Gels are generally more stable and active and water-based gel being less irritant is more preferred over creams and lotions. Benzoyl peroxide is a broad spectrum bactericidal agent which is effective due to its oxidizing activity. The drug has an anti-inflammatory, keratolytic, and comedolytic activities, and is indicated in mild-to-moderate acne vulgaris. Clinicians must make a balance among desired concentration, the vehicle base, and the risk of adverse effects, as higher concentration is not always better and more efficacious. The main limitation of benzoyl peroxide is concentration dependent cutaneous irritation or dryness and bleaching of clothes, hair, and bed linen.^[14] It can induce irritant dermatitis with symptoms of burning, erythema, peeling, and dryness.^[15] This occurs within few days of therapy and mostly subsides with continued use.

B. Topical retinoids

Retinoids have been in use for more than 30 years. Topical retinoids target the microcomedo–pre-cursor lesion of acne. There is now consensus that topical retinoid should be used as the first-line therapy, alone or in combination, for mild-to-moderate inflammatory acne and is also a preferred agent for maintenance therapy. Its effectiveness is well documented, as it targets the abnormal follicular epithelial hyperproliferation, reduces follicular plugging and reduces microcomedones and both noninflammatory and inflammatory acne lesions.^[16-18] Their biological effects are mediated through nuclear hormone receptors (retinoic acid receptor RAR and retinoids X receptor RXR with three subtypes α , β , and γ) and cytosolic binding proteins. Retinoic acid metabolism blocking agents (RAMBAs) such as liarozole have been developed recently to overcome the emergence of all-*trans*-retinoic acid resistance. Tretinoin, adapalene, tazarotene, isotretinoin, metretinide, retinaldehyde, and β -retinoyl glucuronide are currently available topical retinoids. The most studied topical retinoids for acne treatment worldwide are tretinoin and adapalene. There is no consensus about relative efficacy of currently available topical retinoids (tretinoin, adapalene, tazarotene, and isotretinoin). The

concentration and/or vehicle of any particular retinoid may impact tolerability. Adapalene was generally better tolerated than all other retinoid with which it was compared. Tretinoin has recently become available in formulations with novel delivery systems which improves tolerability. One such product Retin-A Micro (0.1% gel) contains tretinoin trapped within porous copolymer microspheres. Avita, the tretinoin is incorporated within a polyoxypropylene (PP-2). Each of these formulations releases tretinoin slowly within the follicle and onto the skin surface, which in turn reduces irritancy with the same efficacy. The main adverse effects with topical retinoid is primary irritant dermatitis, which can present as erythema, scaling, burning sensation and can vary depending on skin type, sensitivity, and formulations.

C. Topical antibiotics

Many topical antibiotics formulations are available, either alone or in combination. They inhibit the growth of *P. acne* and reduce inflammation. Topical antibiotics such as erythromycin and clindamycin are the most popular in the management of acne and available in a variety of vehicles and packaging.^[19] Clindamycin and erythromycin were both effective against inflammatory acne in topical form in combination of 1–4% with or without the addition of zinc.^[20-22] An addition of topical 2% zinc sulfate and nicotinamide was no different than placebo for the treatment of acne. Topical clarithromycin, azithromycin, and nadifloxacin are available in India, but trials for their efficacy and safety are lacking. Side effects though minor includes erythema, peeling, itching, dryness, and burning, pseudomembranous colitis which is rare, but has been reported with clindamycin. A most important side effect of topical antibiotics is the development of bacterial resistance and cross resistance; therefore, it should not be used as monotherapy.

D. Other topical/new agents

Combination therapy: Benzoyl peroxide has the advantage to prevent and eliminate the development of *P. acne* resistance. Therefore it is being more preferred as combination therapy. Its efficacy and tolerability are enhanced when combined with topical erythromycin or clindamycin, confirmed on various trials. Benzoyl peroxide can be combined with tretinoin and found to be superior to monotherapy. Both the molecules should not be applied simultaneously as benzoyl peroxide may oxidize tretinoin. A combination of topical retinoid and topical antimicrobial is more effective in reducing both inflammatory and non-inflammatory acne lesions than either agent used alone. Topical clindamycin and benzoyl peroxide applied once daily and fixed clindamycin phosphate 1.2% and tretinoin 0.025% in aqueous-based gel formulation used once daily are both found to be effective treatment for acne. Addition of zinc acetate to clindamycin and erythromycin gel showed equivalent efficacy but probably reduces the development of microbial resistance.^[23]

Salicylic acid: It has been used for many years in acne as a comedolytic agent, but is less potent than topical retinoid.

Azelaic acid: It is available as 10–20% topical cream which has been shown to be effective in inflammatory and comedonal acne.

Lactic acid/Lactate lotion: It is found to be helpful in preventing and reduction of acne lesion counts.

Tea tree oil 5%: Initial clinical response with this preparation is inevitably slower compared to other treatment modalities.

Picolinic acid gel 10%: It is an intermediate metabolite of the amino acid, tryptophan. It has antiviral, antibacterial, and immunomodulatory properties. When applied twice daily for 12 weeks found to be effective in both type of acne lesions, but further trials are needed to confirm its safety and efficacy.

Dapsone gel 5%: It is a sulfone with anti-inflammatory and antimicrobial properties. The trials have confirmed that topical dapsone gel 5% is effective and safe as monotherapy and in combination with other topical agents in mild-to-moderate acne vulgaris.^[24]

Oral medications

Oral antibiotics

When treating moderate to severe inflammatory acne and also inflammatory acne that has failed to respond to topical treatment, oral antibiotics are often recommended. It is not recommended to use the oral antibiotic alone; instead, it should be used in conjunction with topical retinoids and/or benzoyl peroxide. In order to avoid the development of antibiotic resistance, long-term therapy (more than 3 to 6 months) should be avoided. Instead, it should be used as a bridge to other oral or topical therapies to prevent the development of this resistance.^[12]

Tetracycline class

The first line oral antibiotics of tetracyclines class are the doxycycline, and minocycline, which are mainly characterized by their anti-inflammatory properties.^[12] Tetracyclines are very helpful for inflammatory acne due to their antibacterial and anti-inflammatory properties; this is notably true for antibiotics belonging to the tetracycline class, which inhibit matrix metalloproteinase activity, cytokine production, and chemotaxis in particular. Tetracyclines are recommended first-line oral treatment for acne because of their anti-inflammatory properties, low cost, simplicity of administration, and favorable safety profile. Minocycline hydrochloride extended-release pills, taken daily at a dose of 1 mg/kg, had equivalent effectiveness to higher dosages and much fewer vestibular side effects than other minocycline preparations.^[25]

Macrolides

Several writers propose reducing the use of erythromycin due to global antibiotic resistance. The strong performance of azithromycin has been investigated in a number of dosage regimens in open-label studies, with

the most prevalent being pulse dosing of three to four doses per month. Gastrointestinal disturbances are the most prevalent adverse effect of macrolides.^[12]

Other oral antibiotics

Treatment with other oral antibiotic groups used to treat acne, such as trimethoprim-sulfamethoxazole, cephalosporins, trimethoprim, and penicillin, are unsatisfactory due to a lack of evidence except in cases when tetracyclines and macrolides are contraindicated.^[12] To decrease the development of antibacterial resistance, several experts advocate avoiding class change when extended therapy with oral antibiotics is required unless otherwise warranted. Still, if a patient's first-line antibiotic fails, it's reasonable to try an antibiotic from a different class.^[26]

Isotretinoin

Although some societally ingrained unfavorable connotations, Oral isotretinoin is typically considered to be safe and well-tolerated. In addition to the treatment of severe recalcitrant acne vulgaris, it is also authorized by the Food and Drug Administration (FDA) for the treatment of moderate acne that is resistant to treatment, acne results in scarring or causes significant psychological distress. In 2017, a meta-analysis concluded that using isotretinoin did not raise the risk of depression. And that isotretinoin therapy reduced depressive symptoms. However, in clinically unstable individuals, rare occurrences of mood aggravation have been observed.^[60] The evidence also suggests that there is no relationship between isotretinoin usage and inflammatory bowel illness.^[12] However, the authors of a Cochrane study published in 2018 concluded that there was insufficient high-quality data to establish that isotretinoin is safe and effective.^[27] Isotretinoin has obvious embryotoxic and teratogenic characteristics, regardless of the fact that it is commonly thought to be safe. As a result, the United States Food and Drug Administration (FDA) monitors its usage using the iPLEDGE Risk Evaluation and Mitigation Strategy based on whether or not they are able to get pregnant; patients are divided into two groups. Girls who are potentially pregnant must utilize abstinence or sexually active patients, two widely approved birth control methods, according to the iPLEDGE. In comparison to combined oral contraceptive (COC), doctors prescribing isotretinoin do not provide enough advice on extremely effective contraceptive options (subdermal implant or intrauterine contraception).^[28]

Hormonal treatment

Hormonal treatment is used to reverse androgen's effects on the sebaceous gland. Oral contraceptives, glucocorticoids, and gonadotropin-releasing hormone (GnRH) agonists are working as anti-androgens or can be used to suppress endogenous androgen synthesis by the adrenal glands or ovary.

Oral contraceptives

Oral contraceptives can help with acne in four main ways. First, they restrict LH production, thereby decreasing gonadal androgen production. Second, they stimulate the production of sex hormone-binding globulin, which decrease the amount of free testosterone in the body. Third, by inhibiting the action of the 5-alpha reductase enzyme, they prevent testosterone from being converted into the more potent Dihydrotestosterone (DHT). Finally, the anti-androgen effect of progestins can inhibit androgen receptors on keratinocytes and sebocytes. The third-generation progestins, such as gestodene (which isn't accessible in the US), desogestrel, and norgestimate, have the least intrinsic androgenic action.^[29]

Glucocorticoids Gonadotropin-Releasing Hormone (GnRH) Agonists

Systemic glucocorticoids in high doses may be beneficial in treating acne vulgaris because of their anti-inflammatory properties. In fact, they are normally reserved for the most seriously affected individuals, and they are frequently used in conjunction with isotretinoin to prevent any possible flare-ups from the start of treatment. Furthermore, due to the numerous possible side effects and recurrences following therapy, these medications are usually only administered for a short time. Steroid acne can occur as a result of long-term usage of glucocorticoids. Glucocorticoids are also indicated in small dosages in female patients with increased serum Dehydroepiandrosterone (DHEAS) linked with an 11- or 21-hydroxylase insufficiency, as well as in other persons who have revealed androgen excess. To suppress adrenal production of androgen, low-dose prednisone or dexamethasone can be taken orally at bedtime.^[30]

Gonadotropin-Releasing hormone agonists

GnRH agonists work by disrupting the cyclic release of gonadotropins from the pituitary gland. Women's ovarian steroidogenesis is suppressed as a result of this. These medications are used to treat ovarian hyperandrogenism. Using GnRH agonists to treat acne and hirsutism in women with or without endocrine issues has been demonstrated to be effective.^[31]

Others

Metformin: In a review of the literature, researchers found some evidence that patients with acne who took metformin with other topical or topical and oral antibiotics had a greater reduction in total lesion counts and inflammatory lesions from baseline compared to their control counterparts, with less adverse effects (e.g., diarrhea and flatulence).^[32]

Dairy: A 2017 longitudinal research discovered correlations between high consumption of full-fat diet and acne, as well as high intake of total dairy.^[33] A meta-analysis of 14 studies discovered a relationship for total dairy, skimmed milk, and full-fat milk, with each

additional serving increasing the risk of acne by 83%, 26%, and 13%, respectively; they also discovered a nonlinear dose-response relationship for total dairy, whole fat-milk, low-fat milk, and skimmed milk, with each additional serving increasing the risk of acne by 83%, 26%, and 13%, respectively. According to a newly published study, there is a link between consuming skim or low-fat milk on a daily basis and the development of acne. In other words, persons who consumed a lot of skimmed or low-fat milk were more likely to suffer from acne. Surprisingly, researchers discovered that this was not the case for persons who consumed full-fat milk.^[34,35]

Physical treatment^[24]

A. Lesion removal

a) Comedones

Both open and closed comedones can be removed mechanically with comedone extractor and a fine needle or a pointed blade. Preprocedure topical retinoid application makes the procedure easier. Gentle cautery and laser puncture of macrocomedones are also useful procedure. The limitations of comedo extraction include incomplete extraction, refilling, and the risk of tissue damage.

b) Active deep inflammatory lesions

Aspiration of deep inflamed lesion may be needed in few cases which are followed by IL steroid injection in cysts and sinus tract.

B. Phototherapy

a) Visible light

They are indicated for mild-to-moderate inflammatory acne. *In vitro* and *in vivo* exposure of acne bacteria to 405-420 nm of ultraviolet free blue light results in the photo-destruction through the effect on the porphyrin produced naturally by *P. acne*. Use of limited spectrum wavelength, such as blue light (peak at 415 nm), and mixed blue and red light (peak at 415 and 660 nm) have been found to be effective in reducing acne lesions after 4-12 weeks.

b) Photodynamic therapy

(With addition of δ -aminolevulinic acid) and pulsed dye laser (585 nm) were also effective in acne, but further trials are needed to confirm the same. Physical treatment of scars Acne scar can be broadly divided into two groups, those involving tissue losses (Ice pick scar, Box scar, Rolling scar, and Follicular macular atrophy) and those involving tissue excess (hypertrophic scars or keloids). Currently available treatment for scars include simple excision, and suturing, either alone or combined with punch grafting and laser resurfacing, dermabrasion, various type of lasers, chemical peels, and fillers. For hypertrophic scars, treatment includes pressure therapy, IL corticosteroid, 5-fluorouracil and bleomycin injections, surgical excision, radiotherapy, laser therapy and cryotherapy. All the procedures have their own merits and demerits; to be chosen carefully seeing the merit. Acne and diet Dietary restriction has not been

demonstrated to be benefit in the treatment of acne. The myth that diet affects acne is widespread, but previous studies are not supporting it. Of late, various authors again claiming that there is the definite role of diet in acne but to conclude that further controlled trials are needed. It has been shown that the prevalence of acne is lower in rural, no industrialized societies than in modernized western populations may be due to lower glycemic index diet, claims one trial. Although not currently recognized within our dermatology standard of care, but due to “consistent and good quality patient oriented evidence”, dietary management of acne appears to be accumulating. The benefit of dietary management in the treatment of acne has been neither demonstrated nor disproved.

CONCLUSION

Acne vulgaris is among the most frequent chronic skin disorders. Acne has been studied in terms of the illness itself as well as present and potential acne treatment solutions. Acne therapy focuses on the four pathogenic elements that cause this disease. We reviewed in this work many choices for acne therapy, such as topical as the first-line therapies, and for more severe cases, the systemic and hormonal therapies are more effective. However, we must be aware of the increasing hazard of *P. acnes* becoming resistant to currently available antibiotics. As a result, more study in this sector will always be necessary, and new therapeutic options will be required.

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