

Vehicles and Formulas:

Acne Review

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Acne impacts a large portion of the population with one study reporting 85% of teenagers and 9.4% of the global population generally being impacted by acne. Though acne often impacts teenagers, it can occur in almost any age group and persist into adulthood.^{1,2} Acne can have a significant impact on the quality of life for affected patients and management of this condition can be important for self-esteem. Acne vulgaris is a disease of the pilosebaceous unit, which consists of the hair shaft, hair follicle, sebaceous gland, and erector pili muscle. Acne vulgaris can present as noninflammatory lesions such as open and closed comedones, or inflammatory lesions, such as papules, pustules, and nodules.¹

Common pathogeneses of acne include follicular keratinization, increased or altered sebum production (as a result of androgens), follicular colonization of bacteria, and various inflammatory mechanisms.^{3,4} Acne presentation and causes are often multimodal, and an array of subtly different classifications abound often differentiated by age and sex of the patient as well as microbiologic and endocrine testing where available. This review will focus on topical treatments used in the management of some of the more common varieties of acne. The most common topical options include benzoyl peroxide, topical antibiotics (clindamycin, erythromycin, tetracycline, doxycycline, minocycline, dapsone etc), retinoids (tretinoin, adapalene, tazarotene, etc), keratolytic ingredients (azelaic acid, salicylic acid etc.), and antiandrogenic treatments (spironolactone, clascoterone) among others. Many active pharmaceutical ingredients act through more than one mechanism on acne, for example, retinoids can improve acne both through sebum reduction and through their keratolytic properties and azelaic acid can improve acne through keratolytic activity but also through reduction of inflammation and some antibacterial properties.

The American Academy of Dermatology 2024 Working Group recommends benzoyl peroxide, retinoids, or combination topical antibiotic treatments as first line for mild acne and a mix of oral and topical combination product options for moderate to severe acne. Alternative agents such as clascoterone, salicylic acid, and azelaic acid are recommended as well, though are conditional as opposed to the clearcut recommendations for benzoyl peroxide, retinoids, antibiotics and combinations thereof.^{1,4}

Benzoyl peroxide is a commonly used OTC agent used generally at concentrations between 2.5-10%. It is available as a cream, gel, wash, and even foam. Its mechanism of action is primarily via the generation of reactive oxygen radicals that can kill *Cutibacterium acnes* (*C. acnes* – formerly known as *p. acnes*), one of the leading causes of acne, though it has some keratolytic properties as well.⁵ The benefit of benzoyl peroxide is widely accepted and concentrations of 2.5-3% (typically once daily for approximately 12 weeks) have been studied in large vehicle-controlled trials that have demonstrated benefit in tested populations.⁶ Note, though the AAD does recommend combination treatment with retinoids, retinoids such as tretinoin can be prone to oxidative degradation, so combination products may result in decreased efficacy of tretinoin outside of special

circumstances, such as the commercially available combination product which encapsulates tretinoin in microspheres to protect it from benzoyl peroxide.^{1,7}

Salicylic acid is another common OTC agent. Typical strengths are between 0.5-2% in OTC preparations, though higher strengths are sometimes used. Its mechanisms of action are thought to be through keratolytic action and the reduction of sebum.⁸ Salicylic acid is also used as a penetration enhancer at this concentration and has utility in combination creams for this reason. Salicylic acid is generally best suited to mild or moderate acne and though there is less information on efficacy as compared to benzoyl peroxide, it has demonstrated benefit in comparison studies when used 1-3 times daily and is generally well-tolerated.⁹ Unlike benzoyl peroxide, salicylic acid is not known to interact directly with oxidation prone retinoids such as tretinoin.

Topical antibiotics are recommended by the AAD and are a mainstay of acne treatment. Clindamycin is most commonly used at 1% and erythromycin at 2%.¹ Both clindamycin and erythromycin inhibit bacterial protein synthesis via binding to the 50S ribosomal subunit. Erythromycin is largely bacteriostatic, though clindamycin can be bactericidal depending on the concentration and microbe being treated. Tetracycline antibiotics are generally used as an adjunctive oral therapy for patients with severe acne, but topical use is sometimes considered. Tetracycline antibiotics work by reversibly binding to the 30S ribosomal unit of bacteria and are considered bacteriostatic agents with efficacy against both gram-positive (like *C. acnes*) and negative bacteria. Studies of tetracycline 3% applied twice daily for 8 weeks showed a statistically significant reduction in inflammatory acne lesions.¹⁰ Topical minocycline foam 4% used once daily for 12 weeks also demonstrated improvement in inflammatory and noninflammatory acne lesions.¹¹ Studies on topical doxycycline for acne are limited, though there is a theoretical benefit. Dapsone is another antibiotic used topically for acne. It is available as a 5% gel for twice-daily use or as a 7.5% gel for once daily use. It is unique from the other topical options as its mechanism of action is competitive inhibition of para-aminobenzoate thereby inhibiting bacterial synthesis of dihydrofolic acid. Dapsone has good activity against gram-positive bacteria and has anti-inflammatory properties.¹³

The AAD working group emphasizes that topical antibiotics are not to be used alone for management of acne. The common microbial cause of acne, *C. acnes*, has gained resistance to various antibiotics in recent years. One study reported up to 40% resistance of *C. acnes* to erythromycin, clindamycin, and tetracycline.¹⁸ Another study from 2020 of samples from 100 patients found 73% resistance to erythromycin, 59% to clindamycin, 37% to doxycycline, 36% to tetracycline 31% to trimethoprim/sulfamethoxazole, 15% to levofloxacin, and 3% to minocycline.¹⁹ Benzoyl peroxide or retinoids are often combined with antibiotics to increase efficacy and to reduce resistance. Studies have demonstrated increases in in-vivo antimicrobial effect with combination products such as clindamycin/tretinoin as compared to the use of clindamycin or tretinoin alone.^{20,21} Another study evaluating combination therapy and noting total and inflammatory lesion counts evaluated combination clindamycin/salicylic acid, dapsone/adapalene, and erythromycin/zinc acetate and found the combinations to be more effective than the antibiotic alone in each case.²²

Retinoids are first-line for mild to moderate acne and represent one of the most recommended topical options for acne. Tretinoin between 0.015 and 0.1%, adapalene 0.1 to 0.3%, and tazarotene 0.05 to 0.1% in cream, gel, or foam form are commonly used. Trifarotene, a newer fourth generation retinoid, is used at 0.005%. Retinoids have anti-inflammatory properties and are thought to decrease cohesiveness of follicular epithelial cells resulting in a reduction in microcomedone formation. Furthermore, retinoids are also thought to stimulate mitotic activity and therefore increase turnover of epithelial cells.

Topical retinoids have been proven to be superior in multiple placebo-controlled trials and combination products have demonstrated the ability of retinoids to enhance the efficacy of other agents. Retinoids like adapalene and tazarotene are more stable than tretinoin when combined with benzoyl peroxide. The AAD working group concludes that modest differences in efficacy, tolerability, and activity are not significant enough to suggest superiority of one retinoid over another.⁴ However, on a patient specific level minor differences between retinoids may be considered. Comparison data is difficult to draw conclusions from as many retinoids are available in different strengths and formulations. One study comparing tazarotene 0.045% lotion to adapalene 0.3% gel and trifarotene 0.005% cream found a statistically significant difference in tolerability favoring tazarotene and adapalene as compared to trifarotene.²³ Another study comparing adapalene 0.1% gel to tretinoin 0.025% cream to tazarotene 0.1% gel applied once daily for 12 weeks found the patients on adapalene 0.1% reported better tolerability and patient satisfaction. Patients on tazarotene reported the lowest tolerability and patient satisfaction, though differences between all three groups were minor. The study did not note statistically significant differences in efficacy between treatments.²⁴ A separate small study of tazarotene 0.05% and adapalene 0.1% applied nightly for 8 weeks found tazarotene to be more efficacious but more poorly tolerated.²⁵ Tretinoin has also been compared to adapalene directly with on small trial finding that adapalene 0.1% was more efficacious and better tolerated than tretinoin 0.04%.²⁶ The variety of strengths and formulations compared in these handful of head-to-head trials make conclusions on overall efficacy and tolerability difficult to ascertain. However, it may be that tazarotene and adapalene are slightly more efficacious than tretinoin and that of the retinoids, adapalene may be the best tolerated. For patients who struggle with adverse reactions to retinoids (such as dry skin or irritation), it is sometimes recommended to start out with every other day application for a week or two or to have patients wash their face 30-60 minutes after application.¹² It is important to emphasize the use of sunscreen while applying topical retinoids as they can increase sensitivity to the sun.

Azelaic acid is another popular option for the management of acne. It is an anti-inflammatory agent with antioxidant and some antimicrobial properties commonly used in a cream, gel, or a foam at concentrations ranging from 15-20%.²⁷ Azelaic acid's multimodal mechanism of action allows it to treat other dermatological conditions such as rosacea and hyperpigmentation as well. Patients suffering from acne-induced post inflammatory hyperpigmentation may especially benefit from the use of azelaic acid.^{1,28} A three month long double-blind trial of azelaic acid 20% vs tretinoin 0.05% found them to be equally efficacious for the reduction of comedones and both were superior to placebo. The azelaic acid group had fewer adverse events than the tretinoin group.¹⁷ Another head-to-head randomized, single-blind, parallel-group trial compared the efficacy and tolerability of benzoyl peroxide 3% and clindamycin 1% in combination applied once daily with azelaic acid 20% applied twice daily over a 4-week period. This study found superior efficacy and tolerability with the combination product over azelaic acid alone, though both products significantly improved parameters such as inflammatory lesion count.²⁹ Azelaic acid has also been studied in a limited capacity in combination with other treatments. One double-blind, randomized trial of azelaic acid 5% in combination with clindamycin 2% over a 12-week period found the combination product to significantly reduce the acne severity index as compared to treatment with either agent individually. Additionally, a statistically significant portion of patients preferred combination treatment to treatment with either ingredient alone.³⁰

Salicylic acid, a beta hydroxy acid with keratolytic properties, is another ingredient conditionally recommended by the AAD working group for treatment of acne. Common concentrations range from 0.5-2% and it has been studied both on its own and in combination with other ingredients for topical use for acne.⁴ Topical salicylic acid alone has modest utility, with one randomized controlled trial of salicylic acid 0.5% finding 25% reduction in inflammatory lesions and 11% reduction in open comedones as compared to vehicle over a 12 week period,

but combination studies have noted enhanced benefit.⁴ One study on combination clindamycin 1% and salicylic acid 2% twice daily compared to clindamycin 1% twice daily alone or clindamycin 1% in combination with tretinoin 0.025% once daily over 12 weeks found significant improvements in total lesion count and acne severity index with combination clindamycin and salicylic acid treatment. In fact, salicylic acid/clindamycin was not only superior to clindamycin alone, it was also numerically superior to the tretinoin/clindamycin combination in terms of the acne severity index, though the difference between these groups did not quite reach the level of statistical significance.³⁵ Salicylic acid has also been studied in higher concentrations (such as 20-30%) in peels for management of acne. These peels are typically applied once every 2-4 weeks for between 3 and 6 sessions. Salicylic acid peels are typically either made in alcohol or polyethylene glycol, with polyethylene glycol being preferred by some practitioners as it causes less salicylic acid to be absorbed through the skin and may be better tolerated. Salicylic acid peels may also help with hyperpigmentation associated with acne.³⁶

In addition to beta hydroxy acids such as salicylic acid, alpha hydroxy acids such as lactic or glycolic acid are also sometimes used for acne. Glycolic acid has been studied at lower concentrations (5-10%) for daily use, and higher concentrations (most commonly 30-70%) for peels for acne and hyperpigmentation associated with acne. One study of glycolic acid 5% over four weeks found glycolic acid to improve skin hydration, increase skin brightness/reduce redness, and to improve mild to moderate acne.³⁷ Another randomized double-blind, placebo-controlled trial of glycolic acid 10% applied once daily for 90 days found statistically significant benefit over placebo for mild acne and no difference in tolerability between the placebo and treatment groups.³⁸ When used as a peel, typically treatments are applied every 3-7 days for 4-6 weeks of treatment depending on peel depth and whether the product is being applied at home or in a clinic. Glycolic acid peels require neutralization after application.³⁶

Lactic acid, another alpha hydroxy acid, has also been studied for topical use for acne. Though limited data comparing glycolic acid to lactic acid exists, some studies suggest lactic acid may have superior tolerability to glycolic acid, though this may come at the cost of lower efficacy.³⁹ Much like glycolic acid, lactic acid may be used at lower concentrations (such as 5%) for daily use, or higher concentrations in peels (such as 14% when part of Jessner's Solution combination peel or up to 92% (pure lactic acid solution) when used on its own).³⁶ One study of lactic acid 5% applied twice daily as a preventative measure for acne found significant reduction in both inflammatory and non-inflammatory lesions over the treatment period.⁴⁰ Lactic acid peel usage varies, some higher concentration peels are applied every other week for multiple treatments, with some studies looking at as many as 7 treatments.⁵¹ Combination products like Jessner's Peel is sometimes used every 3 weeks for up to 6 sessions.⁵²

Topical vitamins are also sometimes used as solo agents or adjunct treatment for the management of mild acne, potentially due to their antioxidant properties and for an impact on sebum production. One study of niacinamide (a vitamin B3 derivative) 4% on mild to moderate acne noted that patients who used niacinamide gel for 8 weeks had a statistically significant number of fewer lesions by the end of the treatment, and the product was well tolerated by the patients who did apply it.⁴¹ Another trial evaluated niacinamide 5% vs clindamycin 2% twice daily for the management of mild to moderate acne over 8 weeks. The study found both groups to produce a statistically significant improvement in acne severity index, however, the difference between the two groups was non-significant.⁴² Other trials have evaluated combination treatments. One study of niacinamide 5% combined with benzoyl peroxide 2.5% found that after 12 weeks of once daily treatment, the combination of niacinamide and benzoyl peroxide was more effective than benzoyl peroxide alone at reducing both inflammatory and noninflammatory lesion count as well as reduction of sebum.⁴³ Derivatives of ascorbic

acid (used for their superior stability to unmodified ascorbic acid) applied twice daily at 5% have also been evaluated and found to be effective for topical treatment of acne.⁴⁴

Various salts of zinc have been evaluated for the management of acne both topically and orally, though evidence has been mixed. The mechanism of action is not well understood, reduction of inflammation and antimicrobial activity against *C. acnes* have been cited as potential reasons for zinc's utility for acne.⁴⁵ One study of zinc acetate 1.2% in combination with erythromycin 4% applied twice daily found the combination to be statistically superior to placebo and equally effective as oral tetracycline over a 10-week period.⁴⁶ Another double-blind placebo-controlled trial on zinc sulfate 2% solution applied three times daily failed to show benefit over placebo at 12 weeks.⁴⁷ A more limited study at a higher concentration (zinc sulfate 5%) did note benefit over placebo.⁴⁸ More data is needed to determine the potential role of topical zinc for the management of acne.

For acne known or suspected to be related to androgen imbalance, agents like spironolactone are commonly used orally and occasionally used topically. Spironolactone has anti-androgenic properties and can block the activity of 5 alpha reductase and inhibit dihydrotestosterone receptors in sebaceous glands.^{14,16} The AAD 2024 working group on acne conditionally recommended spironolactone orally at doses ranging from 50-200mg, but does not address topical use.⁴ One pilot clinical trial evaluating spironolactone 5% applied twice daily for 8 weeks in male and female patients with mild to moderate acne found a statistically significant decrease in the number of acne lesions as well as improvement in the acne global grading score.³¹ Limited small studies looking at absorption from topical application of spironolactone suggest minimal if any systemic absorption, indicating that topical treatment may be reasonable for those looking to avoid systemic adverse effects associated with oral spironolactone.⁵³

Clascoterone is another treatment aimed at managing androgen induced acne. Clascoterone is an androgen receptor inhibitor that also works by inhibiting DHT activity in the sebaceous glands. Though studies comparing clascoterone topical to spironolactone topical are not available, data comparing oral spironolactone 200mg to topical clascoterone 1% applied twice daily found both treatments to be effective, though spironolactone 200mg did appear to be the most effective at total lesion count reduction.³² Another head to head trial of clascoterone 1% vs tretinoin 0.05% applied once daily at bedtime for 8 weeks found clascoterone to reach the marker of 50% improvement faster than tretinoin, though, the difference in total lesion count did not reach the level of statistical significance.^{33,34} Clascoterone was conditionally recommended by the AAD 2024 working group because though it did appear to be successful for the treatment of acne, the cost was such that it may not be suitable for all patients.

Limited data also exists on some plant-based therapies including green tea extract and tea tree oil products. Green tea extract products are thought to help with the treatment of acne via their anti-inflammatory properties as well as their impact on reducing sebum production. Various small-scale studies have looked at green tea extract between 1-5%. A split face trial evaluating epigallocatechin gallate (EGCG, green tea extract) 1% vs 5% vs placebo applied twice daily over an 8 week period found significant reduction in both inflammatory and non-inflammatory lesions with green tea extract products, and though the 5% product was numerically superior in terms of acne severity score to the 1% product the difference did not reach the level of statistical significance. Another study looking at 2% green tea lotion applied twice daily over a 6-week period found significant reductions in total lesion count compared to baseline, though, the study did not have a placebo group comparator.⁴⁸ Tea tree oil has also been studied for mild to moderate acne. The proposed mechanism of action is related to the antimicrobial and anti-inflammatory properties of tea tree oil. One double-blind, placebo-controlled trial of 5% tea tree oil gel twice daily over a period of 45 days found significant reductions in total lesion count as well as acne severity score as compared to placebo.⁴⁹ A comparative study looking at tea tree

oil 3%, propolis 20%, and aloe vera 10% gel vs erythromycin 3% cream over a period of 30 days found the combination product to be superior to erythromycin at reduction of erythema scars, acne severity index, and total lesion count.⁵⁰

Acne can be a multifaceted condition, and it often requires a multifaceted approach calling for a combination of treatments. When combining therapies, dosing pattern of the active ingredients, chemical and physical compatibility, and overlapping mechanisms of action should be considered. For example, retinoids are typically dosed once daily at night, so combinations of retinoids with other active ingredients are typically dosed just once daily. Benzoyl peroxide is a strong oxidizer and may be hostile to some active ingredients, so its combination with active ingredients that are prone to oxidation, such as tretinoin, should be avoided. With regards to mechanism of action, studies have shown that various combination products are often superior to treatments with a single active ingredient, for example, patients may benefit from combination antibiotic and a keratolytic or agent to help with sebum control. All of these factors indicate that compounded combination therapy can play an important role in the treatment of acne topically, especially for patients who do not see results or who do not see sufficient results on commercially available products.

Vehicle	Water Activity	Utility for Hyperpigmentation Formulas
Cleoderm	>0.6	A smooth white cream base containing plant-based anti-inflammatory and peptide ingredients. Cleoderm has been demonstrated to be noncomedogenic in clinical testing. Cleoderm also has limited BUD data to support use with some ingredients used for acne treatment such as adapalene, benzoyl peroxide, and azelaic acid. Cleoderm can tolerate high API load of common ingredients used for acne such as azelaic acid and is robust enough to serve as a vehicle for peel formulations as well.
Nourivan Antiox	>0.6	A smooth white oil in water cream base that already contains antioxidants for the stabilization of oxidation prone ingredients such as some retinoids. Nourivan Antiox can tolerate high API load of common ingredients used for acne such as azelaic acid and is robust enough to serve as a vehicle for some peel formulations as well.
Versatile	>0.6	A smooth, white, aqueous cream base with a high API load tolerance and vanishing properties that make it cosmetically elegant for use on the face. This vehicle is robust enough to tolerate high loads of active ingredients commonly used for acne.

Formula ID	Formula Name
FA-24058	Azelaic Acid 15% - Niacinamide 4% Cream (Cleoderm™)(BUD Study)
FA-24057	Adapalene 0.3% - Benzoyl Peroxide 5% Cream (Cleoderm™)(BUD Study)
FA-24060	Niacinamide 4% - Tretinoin 0.025% Cream (Cleoderm™)(BUD Study)
FA-23065	Glycolic Acid 5% - Clindamycin 1% Cream (Cleoderm™)
FA-22858	Dapsone 5% - Tazarotene 0.1% Cream (Nourivan™ Antiox)
FA-22553	Spironolactone 5% - Dapsone 2% - Niacinamide 2% Cream (Versatile™)
FA-23100	Spironolactone 5% Cream (Cleoderm™)
FA-23012	Epigallocatechin Gallate (EGCG) 5% Cream (Cleoderm™)
FA-23062	Ascorbic Acid 10% - Glycolic Acid 2% Cream (Cleoderm™)
FA-22445	Minocycline 4% - Niacinamide 4% Cream (Cleoderm™)
FA-22444	Azelaic Acid 5% - Niacinamide 4% - Erythromycin 2% Cream (Cleoderm™)
FA-22441	Clindamycin 2% - Niacinamide 4% - Benzoyl Peroxide 5% Cream (Cleoderm™)

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