Acne Agents, Topical Review

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FDA-approved Indications

All products included in this review are indicated for the topical treatment of acne vulgaris. Tazarotene (Tazorac) is additionally indicated for the treatment of plaque psoriasis. Sodium sulfacetamide/sulfur (Clarifoam EF) is additionally indicated for topical control of acne rosacea and seborrheic dermatitis.

Drug	Manufacturer
adapalene (Differin®)[1]	Galderma
adapalene/benzoyl peroxide (Epiduo™)[2]	Galderma
azelaic acid (Azelex®)[3]	Allergan
benzoyl peroxide (Benzefoam™)[4] (Clinac™ BPO)[5] (Inova™)[6] (Lavoclen™)[7] (Neobenz™ Micro)[8] (Zaclir™)[9]	generic Onset Therapeutics Ferndale JSJ Pharmaceuticals Prasco SkinMedica Hawthorn
benzoyl peroxide/clindamycin (Acanya™)[10] (BenzaClin®)[11] (Duac® CS)[12]	generic Valeant Sanofi-Aventis GSK
benzoyl peroxide/ erythromycin (Benzamycin® Pak)[13]	generic
benzoyl peroxide/salicylic acid (Inova™ 4/1, 8/2)[14]	JSJ Pharmaceuticals
benzoyl peroxide/sulfur (NuOx)[15]	generic WraSer
clindamycin (Clindagel®)[16] (ClindaReach™)[17] (Evoclin™)[18]	generic Galderma DUSA GSK
dapsone (Aczone™)[19]	Allergan
erythromycin (Akne-Mycin®)[20]	generic
sodium sulfacetamide (Klaron®)[21]	generic
sodium sulfacetamide/sulfur (Clarifoam® EF)[22]	generic
tazarotene (Tazorac®)[23,24]	Allergan
tretinoin (Atralin™)[25] (Retin-A Micro®)[26]	generic Coria Labs OMJPI
clindamycin/tretinoin (Ziana™)[27]	Medicis

Overview

Acne vulgaris is the most common cutaneous condition in the United States. It is a disorder that affects primarily teenagers and young adults, but it can sometimes persist beyond young adulthood. In adolescence, sebaceous glands increase sebum release after puberty. Small cysts called comedones form in hair follicles due to blockage of the pore from accumulated sebum and keratinous material. Bacteria, most often *Propionibacterium acnes*, releases free fatty acids from sebum within the comedones, which causes inflammation to form a cyst. This results in rupture of the cyst wall and subsequent inflammatory reaction due to extrusion of oily and keratinous debris from the cyst.

Classification of the severity of acne is not standardized in the published medical literature.[28] One method of classification is to evaluate the number and type of lesions. There are three categories of the severity of acne and includes either acne occurring on the face or the trunk of the body. These categories are graded as mild, moderate, or severe depending on the presence and number of lesions, which consist of comedones, papules, pustules, and/or cysts. Mild acne is defined by the presence of fewer than 20 comedones, fewer than 15 inflamed papules, or fewer than 30 lesions consisting of the combination comedones and papules. Moderate acne is defined by the presence of 15-50 papules and pustules in addition to comedones and rare cysts, and the total number of lesions on the face can range from 30-125. Severe acne is defined by the presence of mostly inflamed nodules and cysts and includes more than 125 lesions consisting of comedones, papules, and pustules.

The elimination of lesions is the goal of treatment. This is achieved by decreasing sebaceous gland activity, bacterial population, and inflammation. The available products work by different mechanisms to attack the causative events. Typically, retinoids such as tretinoin (Atralin, Retin-A Micro), adapalene (Differin), and tazarotene (Tazorac) are used to inhibit comedone formation and an antibiotic such as clindamycin or erythromycin suppresses *P. acnes*. Combination therapy is useful to limit growing resistance to antibacterial therapy, as well as enhance the efficacy of antibiotics by improving penetration into the lesions.[29,30,31] Since 1990, prescribing has trended more toward agents not reliant on antibacterial mechanisms.[32]

The American Academy of Dermatology (AAD) updated guidelines for the management of acne vulgaris in 2007.[33] The guidelines recommend topical therapy as standard of care in mild to moderate acne treatment and indicate that retinoids, benzoyl peroxide, and benzoyl peroxide in combination with either erythromycin or clindamycin are effective acne treatments. Per the 2009 update to the consensus guidelines developed by the Global Alliance to Improve Outcomes in Acne, the topical retinoids should be the foundation of treatment in most patients with acne as they target the microcomedone, the precursor to all acne lesions.[34,35] When used from the beginning of therapy, retinoids significantly increase the speed of resolution of acne lesions. For inflammatory lesions, an antimicrobial agent (e.g. benzoyl peroxide) or antibiotic can be added for synergy and faster clearing. Prolonged use of antibiotics for acne, both oral and topical, can increase selective pressures on microbial flora, not just *P. acnes*. This prolonged antibiotic use can also lead to the development of resistant staphylococci. Therefore, a limited duration of antibiotics is recommended. In addition, antibacterial monotherapy is avoided due to the concern for development of bacterial resistance.

Combination therapy is useful for mixed lesions as well as other cases with differing severity.[36,37,38,39,40] The 2009 acne consensus guidelines state that combination of a retinoid and antimicrobial is the preferred approach for most patients with acne.[41] This combination results in increased efficacy and faster clearing since the agents target multiple pathophysiologic factors.

But, combination therapy can also increase the incidence and severity of adverse effects. Fixed-dose combination products improve patient convenience and potentially adherence. A formulation without an antibiotic is preferred to minimize bacterial resistance. Retinoid monotherapy or in combination with benzoyl peroxide should be continued as maintenance therapy. If a retinoid/antibiotic combination is used, either benzoyl peroxide should be added to the regimen or therapy should be changed to a retinoid with or without benzoyl peroxide upon resolution of inflammatory lesions. Similarly, antibiotic/benzoyl peroxide combinations are not ideal for maintenance therapy.

Benzoyl peroxide has bactericidal, keratolytic, and comedolytic activity and has been useful as a single agent and in combination with antibiotics or retinoids in decreasing the number of lesions in mild to moderate acne.[42] Combining a topical antibiotic with benzoyl peroxide reduces the development of resistant strains of *P. acnes*.[43,44,45] However, due to antibiotic resistance, as soon as inflammatory lesions begin to resolve, antibiotics should be discontinued.[46] This combination is more effective and less irritating than benzoyl peroxide used alone. There are many different strengths and formulations available for benzoyl peroxide. It is unknown if there is increased efficacy from higher or lower concentrations of the products, but the incidence of adverse effects may increase with greater concentration of drug.

Clindamycin has been associated with greater incidences of adverse effects when introduced into the systemic circulation compared to erythromycin, but the topical application of these products allows for minimal systemic absorption. There does not appear to be any significant differences in the efficacy of these topical antibiotics. Monotherapy with these topical antibiotics is not recommended due to the development of bacterial resistance.[47,48]

Azelaic acid (Azelex) exhibits comedolytic and antibacterial properties; it is not viewed as initial therapy.[49] Investigation of clinical efficacy for sodium sulfacetamide is lacking, as are the effects of combinations with sulfur. Sulfur is an older therapeutic agent exhibiting antimicrobial and keratolytic activity, and has demonstrated some usefulness in the treatment of acne.[50,51] The clinical evidence, however, demonstrating the efficacy of sulfur in acne treatment has not been consistently or reliably proven. Dapsone (Aczone) is a topical sulfone developed from the oral formulation which is used to treat leprosy.[52] Although the safety and efficacy have been evaluated over a 12-month period, dapsone should be reserved for second line therapy.[53]

Adapalene and tazarotene have been shown to be at least as effective as tretinoin, often with a lower incidence of adverse effects.[54] However, tazarotene gel may be more irritating than tretinoin or adapalene. The tazarotene cream formulation may be better tolerated, but how it compares in effectiveness with adapalene or tretinoin remains to be determined.

Systemic treatment is generally required in cases of severe acne, and hormonal therapy is available for females. This review focuses on the available topical preparations for acne treatment.

Pharmacology[55]

Clindamycin and erythromycin are antibiotics that inhibit bacterial protein synthesis at the ribosomal level by binding to the 50S ribosome and affecting the process of peptide chain initiation. They have been shown to have *in vitro* activity against *P. acnes*, an organism commonly associated with acne vulgaris. Antagonism has been reported between clindamycin and erythromycin. Sulfonamides such as sodium sulfacetamide (Klaron, Clarifoam EF) probably work by acting as a competitive inhibitor of para-aminobenzoic acid utilization (PABA). PABA is an essential component for bacterial growth.

Benzoyl peroxide has a keratolytic and desquamative effect that may contribute to its efficacy. Benzoyl peroxide is bactericidal with activity against *P. acnes*, which is believed to be due to its oxidizing properties. It is available in combination with other agents such as antibiotics and sulfur, which contributes a mild keratolytic action. Salicylic acid causes desquamation of hyperkeratotic epithelium.

The exact mechanism of action of azelaic acid (Azelex) is not known. It has been shown to have antibacterial activity against *P. acnes* and *Staphylococcus epidermidis*, as well as a normalization of keratinization that leads to an anticomedonal effect.

The exact mechanism of action of dapsone (Aczone) in the treatment of acne vulgaris is unknown, but *in vitro* studies suggest that it may suppress neutrophil recruitment oxidation, which may help prevent the production of toxic respiratory and secretory products. It may also have antimicrobial activity.

Tazarotene (Tazorac) is a retinoid prodrug that, when activated, has antihyperproliferative, differentiation normalizing, and anti-inflammatory effects. The exact mechanism of action is unknown. Tretinoin (Atralin, Retin-A Micro), another retinoid, works by decreasing cohesiveness of follicular epithelial cells and decreasing microcomedone formation. It may also stimulate mitotic activity and increase turnover of follicular epithelial cells, causing extrusion of the comedones. Adapalene (Differin, Epiduo) is a modulator of cellular differentiation, keratinization, and inflammatory processes. Although the exact mechanism of action is unknown, adapalene may normalize the differentiation of follicular epithelial cells, resulting in decreased microcomedone formation.

Pharmacokinetics[56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85]

Clindamycin is only one percent available systemically when administered topically. The low levels seen in the plasma are excreted unchanged in the urine.

Topically administered erythromycin is not detectable in the plasma.

Less than two percent of benzoyl peroxide is absorbed in the systemic circulation. Due to the lipophilic nature, benzoyl peroxide concentrates in the lipid-rich sebaceous follicles. The small amount that is systemically absorbed is converted to benzoic acid, which is further metabolized to benzoate. Benzoate is then excreted in the urine.

The systemic exposure to dapsone 5% gel (Aczone) versus oral dapsone 100 mg was studied for 14 days. The results indicated that twice daily topical application of the agent leads to less systemic exposure to the drug than the 100 mg once daily oral administration of the drug. Patients applying the drug topically had approximately 100-times less exposure to the active drug, as measured by the area-under-the curve (AUC), than patients taking the drug orally.

Tazarotene (Tazorac) is converted by ester hydrolysis to its active metabolite, tazarotenic acid. There is little parent compound absorbed in the plasma, and the small amount is highly plasma protein-bound. Tazarotenic acid is eliminated by the urinary and fecal routes. Its half-life is about 18 hours.

Tretinoin (Atralin, Retin-A Micro) has only been found in trace amounts in plasma when applied topically. It is a metabolite of Vitamin A.

Sulfacetamide (Klaron) is about four percent bioavailable and is excreted in the urine unchanged. The half-life of sulfacetamide varies between seven and 13 hours. Absorption through intact skin has not been determined for sodium sulfacetamide (Clarifoam EF).[86] Approximately one percent of topical sulfur is systemically absorbed.

Pharmacokinetic studies with adapalene (Differin) and the combination product with benzoyl peroxide (Epiduo) have only found trace amounts of adapalene in plasma when administered topically. Excretion is primarily by the biliary route.

Azelaic acid (Azelex) is about four percent bioavailable, and any absorbed drug is excreted unchanged in the urine. Its half-life is about 12 hours.

Contraindications/Warnings[87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116]

Products containing clindamycin or erythromycin (Acanya, Benzaclin, Benzamycin Pak, Duac CS, Cleocin T, Clindagel, Clindareach, Evoclin, Ziana) are contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Sulfacetamide (Klaron, Clarifoam EF) is contraindicated in patients with hypersensitivity to sulfonamides. Sodium sulfacetamide/sulfur is not to be used by patients with kidney disease. Tazarotene (Tazorac) is contraindicated in pregnant women or women who may become pregnant.

Topical dapsone gel (Aczone) is contraindicated in persons with a hypersensitivity to dapsone and any other component in the formulation. Some glucose-6-phosphate dehydrogenase (G6PD) deficient patients using dapsone gel developed laboratory changes suggestive of mild hemolysis. Medication should be discontinued if suggestive signs and symptoms of hemolytic anemia occur. Topical administration of dapsone gel did not demonstrate peripheral neuropathy or skin reactions as reported with oral administration. Oral dapsone has produced dose-related hemolysis and hemolytic anemia.

For patients using adapalene- (Differin, Epiduo), tretinoin- (Atralin, Retin-A Micro, Ziana), or benzoyl peroxide-containing products, excessive or prolonged exposure to sunlight should be limited. Patients taking other photosensitizing medications should use additional caution. Weather extremes such as wind or cold may also be irritating. Patients should use caution to avoid contamination of hair, fabrics, and carpet with benzoyl peroxide products as bleaching and/or discoloration may result.

Erythema, scaling, dryness, and stinging/burning may be experienced with the use of adapalene/benzoyl peroxide gel (Epiduo). These reactions are most likely to occur during the first four weeks of treatment. Reactions are generally mild to moderate in intensity and typically lessen with continued use. Depending upon severity, patients should be advised to use a moisturizer and/or reduce the frequency of application.

Adapalene/benzoyl peroxide gel should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, the use of 'waxing' as a depilatory method should be avoided on skin surfaces treated with adapalene/benzoyl peroxide gel.

Pseudomembranous colitis has been reported with bacterial agents such as clindamycin and erythromycin, ranging in severity from mild to life-threatening, when administered orally or parenterally. Absorption of these antibiotics through the skin is minimal, however.

Concomitant topical acne treatment, as well as cosmetic products with drying effects, should be used with caution, as possible cumulative irritancy may occur.

During the early weeks of therapy, apparent exacerbations of acne may occur. This is caused by the product's action on previously unseen lesions and should not be viewed as a reason to discontinue therapy.

Fatalities have rarely occurred due to severe reactions to sulfonamides such as sulfacetamide. Sulfacetamide also contains sodium metabisulfite, which may cause allergic-type reactions in patients.

Azelaic acid (Azelex) can cause hypopigmentation.

Contact with eyes, eyelids, lips, and mucous membranes should be avoided. Breaks in the skin should also not come into contact with these products.

Avoid fire, flame, and smoking following use of any gel; they are flammable.

Tretinoin (Atralin) gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish.

Drug Interactions[117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146]

Concomitant use with cosmetics, medicated or abrasive soaps and cleansers, alcohol, astringents, spices, or lime grind or other agents that have a strong drying effect should be avoided. Benzoyl peroxide potentiates adverse effects seen with tretinoin during concurrent use.

Levels of dapsone and its metabolites, N-acetyl-dapsone (NAD) and dapsone hydroxylamine (DHA), increased when co-administered with trimethoprim-sulfamethoxazole. Temporary local yellow or orange discoloration of the skin and facial hair was seen when topical administration of dapsone was followed by benzoyl peroxide. Concomitant medications such as rifampin, anticonvulsants, and St. John's Wort may increase the formation of DHA, which is associated with hemolysis.

Topical erythromycin-containing products and topical clindamycin-containing products should not be administered concomitantly due to the potential antagonism of effect. Other concomitant topical acne therapies should be used with caution in order to prevent cumulative irritancies.

Tazarotene (Tazorac) should be administered with caution if the patient is also taking drugs known to be photosensitizers such as thiazides, tetracyclines, fluoroquinolones, phenothiazines, or sulfonamides because of the increased possibility of augmented photosensitivity.

Adverse Effects

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
adapalene (Differin)[147]	10-40	10-40	10-40	10-40	10-40	<1
adapalene/ benzoyl peroxide (Epiduo)[148]	2-27	nr	2-41	2-41	nr	nr
azelaic acid (Azelex)[149]	<1	<1	<1	1-5	1-5	nr
benzoyl peroxide[150]	5	5	nr	nr	nr	nr
benzoyl peroxide (Benzefoam)[151]	nr	nr	reported	nr	nr	nr
benzoyl peroxide (Clinac BPO)[152]	reported	reported	reported	nr	nr	nr
benzoyl peroxide (Inova)[153]	reported	nr	reported	reported	nr	nr
benzoyl peroxide (Lavoclen)[154]	reported	reported	reported	reported	nr	nr
benzoyl peroxide (Neobenz Micro)[155]	nr	nr	reported	nr	nr	nr
benzoyl peroxide (Triaz)[156]	5	5	nr	1-2.5	nr	nr
benzoyl peroxide/ clindamycin (Acanya)[157]	2-25	0.1	nr	1-8	1-15	nr
benzoyl peroxide/ clindamycin (BenzaClin)[158]	1	2	12	nr	2	1
benzoyl peroxide/ clindamycin (Duac CS)[159]	5-26	2-17	1-15	<1-5	nr	nr
benzoyl peroxide/ erythromycin (Benzamycin Pak)[160]	2.5	0.5	7.6	2.5	nr	1.3
benzoyl peroxide/ salicylic acid (Inova 4/1)[161]	reported	nr	reported	reported	nr	nr
benzoyl peroxide/ sulfur (NuOx)[162]	5	5	nr	nr	nr	nr
clindamycin (Cleocin T)[163]	7-16	7-11	18-23	10-11	7-11	nr
clindamycin (Clindagel)[164]	nr	0.6	nr	nr	0.6	nr
clindamycin (Clindareach)[165]	16	11	19	11	7	nr
clindamycin (Evoclin)[166]	nr	nr	1	6	1	nr
dapsone (Aczone)[167]	5-9	6-13	3-14	1	1	nr
erythromycin (Akne-Mycin)[168]	reported	reported	nr	nr	nr	nr
sodium sulfacetamide (Klaron)[169]	<1	nr	nr	reported	<1	nr
sodium sulfacetamide/sulfur (Clarifoam EF)[170]	nr	nr	nr	nr	nr	nr

Adverse effects data are reported as percentages and obtained from package inserts and are not meant to be comparative. During the first weeks of treatment, cutaneous adverse effects may occur. These effects typically lessen with continued use of the product, and are reversible with discontinuation of use. nr = not reported

Adverse Effects (continued)

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
tazarotene (Tazorac)[171,172]	10-30	10-30	10-30	10-30	1-5	reported
tretinoin (Retin-A)[173]	reported	nr	nr	nr	nr	reported
tretinoin (Retin-A Micro)[174]	reported	reported	reported	reported	reported	reported
tretinoin (Atralin)[175]	7	12	16	8	2	1
clindamycin/tretinoin (Ziana)[176]	26	17	1	2-4	4	reported

Adverse effects data are reported as percentages and obtained from package inserts and are not meant to be comparative. During the first weeks of treatment, cutaneous adverse effects may occur. These effects typically lessen with continued use of the product, and are reversible with discontinuation of use. nr = not reported

Special Populations[177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207]

Pediatrics

The safety and effectiveness of all these products in patients younger than 12 years of age have not been established; the exceptions are benzoyl peroxide (Nuox), which has been approved for patients as young as six years of age and tretinoin (Atralin), which has been studied in children as young as 10 years of age.

Pregnancy

Tazarotene (Tazorac) is a teratogenic substance; it is not known what level of exposure causes teratogenicity in humans. Tazarotene is classified as Pregnancy Category X. Other retinoids may cause fetal harm in pregnant women; tretinoin (Atralin, Retin-A Micro), adapalene (Differin), clindamycin/benzoyl peroxide (Acanya), and clindamycin/tretinoin (Ziana) are Pregnancy Category C.

All other reviewed agents are Pregnancy Category C, with the exception of clindamycin and erythromycin products, which are Pregnancy Category B.

Patients with deficiency of glucose-6-phosphate dehydrogenase (G6PD)

A total of 64 patients aged 12 years and older with G6PD deficiency and acne vulgaris were enrolled in a double-blind, randomized, vehicle-controlled, crossover study of dapsone 5% gel or vehicle gel.[208] Patients were randomized to either treatment for 12 weeks with a washout period of two weeks between treatments. All treatments were applied twice daily to the face and to other acne-affected areas. Hemoglobin concentration decreased 0.32 g/dL from baseline to two weeks during dapsone gel treatment. This was not accompanied by changes in other laboratory parameters, including reticulocytes, haptoglobin, bilirubin, and lactate dehydrogenase levels, and was not apparent at 12 weeks as treatment continued. The number of subjects with a 1-g/dL drop in hemoglobin concentration was similar between treatment groups at both week two and week 12. The largest drops in hemoglobin concentration were 1.7 g/dL in the vehicle gel treatment group and 1.5 g/dL in the dapsone gel treatment group. No clinical signs or symptoms of hemolytic anemia were noted.

Dosages

Drug	Instructions	Availability
adapalene (Differin)[209]	apply once daily at bedtime as directed	0.1% cream, gel 0.3% gel
adapalene/ benzoyl peroxide (Epiduo)[210]	apply pea-sized amount to once daily to affected areas after washing	0.1%/2.5% gel
azelaic acid (Azelex)[211]	apply to affected areas	20% cream
benzoyl peroxide[212]	apply once or twice daily as directed	7% gel 2.5, 4.5, 5, 5.25, 5.75, 6.5, 7, 8.5, 10% wash 4.5, 5, 6.5, 8.5, 10% cream 3, 4.5, 6, 6.5, 8.5, 9% cleanser, pads 4% lotion
benzoyl peroxide (Benzefoam) [213]	apply once daily as directed	5.3% emollient foam
benzoyl peroxide (Clinac BPO)[214]	apply once or twice daily as directed	7% gel
benzoyl peroxide (Inova)[215]	apply once or twice daily as directed	4, 8% pad
benzoyl peroxide (Lavoclen) [216]	apply once or twice daily as directed	4, 8% wash
benzoyl peroxide (Neobenz Micro)[217]	apply once or twice daily as directed	3.5, 5.5, 8.5% cream 3.5, 5.5 % single-dose (SD) cream
benzoyl peroxide (Zaclir)[218]	apply once or twice daily as directed	4, 8% lotion
benzoyl peroxide/ clindamycin (Acanya)[219]	apply once daily to the face	2.5%/1.2% gel
benzoyl peroxide/clindamycin (BenzaClin)[220]	apply twice daily or as directed	5%/1% gel
benzoyl peroxide/clindamycin (Duac CS)[221]	apply once daily or as directed	5%/1% gel Convenience pak with 45 gm SFC lotion
benzoyl peroxide/ erythromycin (Benzamycin Pak)[222]	apply twice daily as directed	5%/3% gel
benzoyl peroxide/sulfur (Inova 4/1, 8/2)[223]	apply once or twice daily as directed	4%/1%, 8%/2% benzoyl peroxide/salicylic acid pads
benzoyl peroxide/sulfur (NuOx)[224]	ages 6-12: apply once daily as tolerated ages 12 and older: apply daily during the first week, then twice daily thereafter as tolerated	6%/3% gel
clindamycin[225]	apply twice daily to affected areas	1% gel, lotion, solution, pledgets
clindamycin (Clindagel)[226]	apply once daily to affected areas	1% gel
clindamycin (Clindareach)[227]	apply twice daily to affected areas	1% pads
clindamycin (Evoclin)[228]	apply once daily to affected areas	1% foam
dapsone (Aczone)[229]	apply pea-sized amount twice a day to affected areas	5% gel

Dosages (continued)

Drug	Instructions	Availability
erythromycin[230]	apply twice daily to affected areas	2% gel, pledgets, solution
erythromycin (Akne-Mycin)[231]	apply twice daily to affected areas	2% ointment
sodium sulfacetamide (Klaron)[232]	apply twice daily to affected areas	10% lotion, topical suspension
sodium sulfacetamide/sulfur	apply one to three times daily to affected areas as directed	10%/4% pads 10%/5% lotion, cloth 10%/4% wash with meratan cream kit (Rosula CLK Kit)
sodium sulfacetamide/sulfur (Clarifoam EF)[233]	apply one to three times daily to affected areas as directed	10%/5% emollient foam
tazarotene (Tazorac)[234,235]	apply once daily in the evening to affected areas	0.05, 0.1% cream, gel
tretinoin[236]	apply once daily at bedtime as directed	0.025, 0.05, 0.1% cream 0.025, 0.01% gel
tretinoin (Retin-A Micro)[237]	apply once daily in the evening to affected areas	0.04, 0.1% gel
tretinoin (Atralin)[238]	apply once daily at bedtime to affected areas	0.05 % gel
clindamycin/tretinoin (Ziana)[239]	apply once daily at bedtime to face	1.2%/0.025% gel

Before application of these products, the affected skin should be thoroughly washed, rinsed with warm water, and patted dry.

Benzamycin requires the addition of ethyl alcohol and must be refrigerated following reconstitution.

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and acne vulgaris. Randomized controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There were many studies found using these criteria. Only comparative studies were included, and studies of the active drug compared to placebo were not included. Unacceptable data were determined to be those studies with any of the following characteristics: low number of patients enrolled, comparator drug not available in the U.S., manufacturer-sponsored, open-label, pooled data, unavailable strengths in U.S., use of different formulations of the same active ingredient, inadequate treatment duration, or split-face treatment. Many studies use the investigator-blinded design rather than using the double-blinded method.

adapalene (Differin) and benzoyl peroxide/clindamycin (Duac)

A multicenter, parallel-group, single-blind study of 109 patients measured the efficacy and safety of benzoyl peroxide 5%/clindamycin 1% gel, adapalene 0.1% gel, and the combination.[240] Primary endpoints were inflammatory, noninflammatory, and total lesion counts at weeks two, four, eight, and 12. Lesion count reduction and percentage change at week 12 were highest in the combination therapy group (p=NS) and lowest in the adapalene group (p=NS). Taken individually, the combination group had higher reductions in noninflammatory lesions and total lesions compared to the adapalene group (both $p<0.05$). At week 12, there were no significant differences among groups with regard to erythema, dryness, or peeling. A separate analysis of the adverse events showed that the patients in the combination therapy group had less erythema than patients in the adapalene group ($p<0.05$).

A randomized, assessor-blind study enrolled 130 patients with mild to moderate facial acne vulgaris to compare benzoyl peroxide 5%/clindamycin 1% gel and adapalene 0.1% gel for 12 weeks.[241] Lesion counts, acne grade, and global improvement were assessed at weeks one, two, four, eight, and 12. Both agents were effective, but benzoyl peroxide 5%/clindamycin 1% gel had a faster onset of action and a faster significant reduction in inflammatory and total lesion counts compared with adapalene gel. There was a statistically significant difference for both inflammatory lesions ($p\leq0.001$) and total lesions ($p\leq0.004$), between benzoyl peroxide 5%/clindamycin 1% gel versus adapalene gel, starting at week one and continuing onward. Inflammatory lesions remaining at week two in benzoyl peroxide 5%/clindamycin 1% gel versus adapalene gel were 55 percent versus 76 percent, respectively. At week two, benzoyl peroxide 5%/clindamycin 1% gel removed 38 percent more inflammatory lesions than adapalene gel. The trend in favor of benzoyl peroxide 5%/clindamycin 1% gel continued but was less marked for the remainder of the study. Benzoyl peroxide 5%/clindamycin 1% gel was better tolerated than adapalene gel.

adapalene (Differin) and tazarotene (Tazorac)

A multicenter, double-blind, randomized, parallel-group study enrolled 164 patients with mild to moderate facial acne vulgaris to receive 15 weeks of treatment with alternate-day tazarotene 0.1% gel and vehicle gel on the intervening evenings or once daily adapalene 0.1% gel.[242] Both regimens were comparably effective with no significant between-group differences in efficacy measures. A total of 74 percent of tazarotene-treated subjects and 73 percent of adapalene-treated subjects achieved at least a 50 percent improvement in their acne. In addition, there were no clinically significant differences in tolerability. It appears that tazarotene treatment can be useful even in patients whose compliance may be suboptimal.

The efficacy and tolerability of tazarotene 0.1% gel and adapalene 0.1% gel were compared in a multicenter, double-blind, randomized, parallel-group study in 145 patients with mild to moderate facial acne vulgaris.[243] Both treatments were applied once daily in the evenings for up to 12 weeks. Treatment with tazarotene was associated with a significantly greater incidence of treatment success (≥50 percent global improvement with 78 percent versus 52 percent; $p=0.002$), significantly greater reductions in overall disease severity ($p<0.0001$), non-inflammatory lesion count ($p<0.0001$), and inflammatory lesion count ($p=0.0002$) compared with adapalene. In the early weeks of treatment, tazarotene was associated with greater levels of burning, pruritus, erythema, and peeling compared with adapalene ($p<0.01$); however, at the end of treatment, patients considered both treatments to be comparably well tolerated.

adapalene (Differin) and tretinoin

A dose range effect of two concentrations of adapalene gel as acne treatment was evaluated as well as a comparison of adapalene 0.1% gel with tretinoin 0.025% gel in the treatment of acne patients using two multicenter, investigator-masked, parallel group studies.[244] In the dose range study, 89 patients were enrolled, and 591 patients were in the concurrent controlled studies. Adapalene 0.1% gel was significantly more effective in treating acne lesions than adapalene gel 0.03%. Adapalene gel 0.1% was significantly more effective than tretinoin 0.025% gel in one study and of the same effectiveness in the other study. Adapalene gel was better tolerated than tretinoin gel.

The ten-week, multicenter, randomized, investigator-masked, active-controlled, parallel-group study compared adapalene 0.1% gel with tretinoin 0.05% cream in 409 patients with mild to moderate acne vulgaris.[245] Adapalene 0.1% gel demonstrated equivalent efficacy in reduction of acne lesion counts and global improvement of acne severity over ten weeks. Adapalene 0.1% gel was significantly better tolerated than tretinoin cream 0.05% in terms of erythema, dryness, desquamation, and stinging/burning.

The safety and efficacy of adapalene 0.1% gel compared with tretinoin 0.025% gel were evaluated in 150 Chinese patients with mild to moderate acne vulgaris in an eight-week, multicenter, randomized, controlled, investigator-masked, parallel-group study.[246] The results showed that adapalene 0.1% gel had efficacy equivalent to tretinoin 0.025% gel against acne lesions in Chinese patients, with a more acceptable tolerability profile.

To determine the tolerability and efficacy of adapalene 0.1% gel versus tretinoin 0.1% microsphere gel in 168 patients with acne vulgaris, a 12-week, multicenter, randomized, controlled, investigator-masked, parallel-group study was conducted.[247] The efficacy of adapalene 0.1% gel was comparable to that of tretinoin 0.1% microsphere gel, and both treatments had similar onset of action. Cutaneous tolerability was noted in both groups, with scores significantly better with adapalene 0.1% gel than with tretinoin 0.1% microsphere gel. There were significantly fewer treatment-related adverse events reported with adapalene 0.1% gel.

A randomized, multicenter, investigator-masked study was conducted in 105 patients with mild to moderate acne vulgaris to compare the efficacy and safety of adapalene 0.1% gel with tretinoin 0.025% gel after three months of treatment.[248] In terms of efficacy, adapalene gel was found to be superior to tretinoin gel after one week of treatment, with respect to reduction in inflammatory lesion counts (32 percent versus 17 percent, respectively; p=0.001), total lesion counts (28 percent versus 22 percent; p=0.042), and global severity grade (28 percent versus 16 percent; p=0.001). No significant differences between the two treatments were found after 12 weeks of treatment for any of these variables. Evaluation of facial skin tolerance parameters showed significant differences between the two treatments in favor of adapalene for dryness, erythema, immediate and persistent burning, and pruritus for at least one time point. Quality of life scores improved more rapidly in the adapalene group than in the tretinoin group.

A study was designed to compare the efficacy and safety of adapalene 0.1% gel once daily and tretinoin 0.025% gel once daily in the treatment of facial acne vulgaris.[249] Three hundred twenty-three patients were enrolled for 12 weeks in an investigator-masked, randomized, parallel-group, multicenter trial. Starting at weeks two and four, adapalene produced greater lesion reductions than did tretinoin for all lesion types. By week 12, the mean percent reduction in the different lesion counts was 49 percent versus 37 percent for total lesions (p<0.01); 46 percent versus 33 percent for non-inflammatory lesions (p=0.02); and 48 percent versus 38

percent for inflammatory lesions (p=0.06) in adapalene (Differin) and tretinoin treatment groups, respectively. Adverse effects were limited to a mild dermatitis occurring in both treatment groups.

adapalene/benzoyl peroxide (Epiduo), adapalene (Differin), and benzoyl peroxide

This study was a multicenter, double-blind, randomized study involving 517 subjects who were randomized to adapalene/benzoyl peroxide (BPO) gel, adapalene 0.1% in vehicle gel, BPO 2.5% in vehicle gel, or vehicle gel alone. The median age of these subjects was 15 years and 60 percent were males.[250] At baseline, subjects had between 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions. The majority of subjects had a baseline Investigator's Global Assessment (IGA) of 'moderate', which corresponded to more than half of the face being involved and including many comedones, papules, and pustules. The efficacy results at week 12 showed a two-grade IGA improvement and 'clear' or 'almost clear' rating for 21.5 percent of the adapalene/BPO group, 12.2 percent of the adapalene group, 12.1 percent of the BPO group, and 5.6 percent of the vehicle group.

A 12-week, randomized, double-blind, parallel-group, active- and vehicle-controlled, multicenter trial compared adapalene 0.1%/benzoyl peroxide 2.5% (BPO) gel, adapalene 0.1% in vehicle gel, BPO 2.5% in vehicle gel, or vehicle gel alone in 1,668 patients with moderate facial acne.[251] At 12 weeks, the combination adapalene-BPO gel showed a significantly higher success rate (the percentage of participants with IGA of acne severity rated clear or almost clear; p≤0.006) and a greater percentage reduction in all acne lesion counts (p≤0.017) compared with the other treatment groups. A significant early treatment effect of adapalene-BPO combination gel at Week 1 compared with adapalene monotherapy and vehicle also was observed for all lesion count reductions (p<0.001). Adverse events were similar in all groups.

clindamycin and adapalene (Differin)/clindamycin

A total of 300 patients with acne entered a multicenter, randomized, investigator-blinded study comparing the efficacy and safety of adapalene 0.1% gel combined with clindamycin topical solution 1% versus clindamycin topical solution 1% alone.[252] A statistically significant greater reduction was observed from week four until week 12 in total lesion counts and from week eight on for inflammatory and non-inflammatory lesion counts during the initial treatment for combination therapy compared with monotherapy. In the second part of the study (weeks 12 to 24) which was completed by 241 subjects, the efficacy and safety of adapalene alone as maintenance therapy were investigated. Results at week 24 for the reduction in all lesion counts during the maintenance phase were statistically significant in favor of adapalene (41.6 percent) compared with an increase for all lesion counts in the control group (92.1 percent). Adapalene alone or in combination with clindamycin topical solution was well tolerated.

A multicenter, randomized, investigator-blinded study evaluated the efficacy and tolerability of adapalene 0.1% gel plus clindamycin 1% lotion compared with clindamycin 1% lotion plus vehicle for the treatment of mild to moderate acne vulgaris in 249 patients.[253] Clindamycin was applied twice daily and adapalene or vehicle gel once daily for 12 weeks. A significantly greater reduction of total (p<0.001), inflammatory (p=0.004), and noninflammatory lesions (p<0.001), were seen in the clindamycin/adapalene group than in the clindamycin/vehicle group. These significant treatment effects were observed as early as week four for both non-inflammatory and total lesion counts. The worst scores for scaling (p<0.05), dryness (p<0.01), and stinging/burning (p<0.05) were higher in the clindamycin/adapalene group than in the clindamycin/vehicle group.

benzoyl peroxide/clindamycin, adapalene (Differin), and tretinoin microsphere (Retin-A Micro)

A multicenter, randomized, single-blind study of 353 patients measured the efficacy and safety of benzoyl peroxide 5%/clindamycin 1% gel in combination with either adapalene 0.1% gel or tretinoin microsphere 0.04% or 0.1% gel.[254] The primary endpoint was investigator global assessment, including variables of lesions counts, global disease severity, and disease signs and symptoms. A trend toward greater reduction in lesions at all time points was seen in the tretinoin 0.04% combination patients, but the difference did not reach statistical significance. The same trend was seen in global disease severity and disease signs and symptoms; none of the differences were statistically significant. Adverse events were minimal and mild in each group.

benzoyl peroxide/clindamycin (Acanya), benzoyl peroxide, and clindamycin

The clinical safety and efficacy of benzoyl peroxide (BPO)/clindamycin gel were established in two identical, double-blind, randomized, controlled, 12-week, four-arm studies in which vehicle gels were used as the comparators.[255,256] A total of 2,813 patients with moderate to severe acne vulgaris aged 12 years or older were randomized to receive BPO/clindamycin, BPO, clindamycin, or vehicle. Safety and efficacy (inflammatory and noninflammatory lesion counts) were evaluated using Evaluator Global Severity Score and subject self-assessment. BPO/clindamycin demonstrated superiority to each individual ingredient and vehicle in reducing both inflammatory and non-inflammatory lesions and acne severity. Visibly greater improvement was observed by patients with BPO/clindamycin as early as week two. No substantive differences were seen in tolerability among treatment groups; less than one percent of patients discontinued treatment because of adverse events.

benzoyl peroxide/clindamycin (BenzaClin, Duac), benzoyl peroxide, and benzoyl peroxide/erythromycin (Benzamycin Pak)

In the randomized, ten-week, multicenter, single-blind trial, 492 patients with moderate to moderately severe acne were treated twice daily with benzoyl peroxide 5%/clindamycin 1%, benzoyl peroxide 5%, or benzoyl peroxide 5%/erythromycin 3% and assessed every two weeks.[257] Compared with benzoyl peroxide, benzoyl peroxide/clindamycin demonstrated significantly greater reductions in inflammatory lesions ($p=0.04$) and significantly greater overall improvement as assessed by physicians ($p\leq0.04$) and patients ($p<0.001$). Benzoyl peroxide/clindamycin was not significantly more efficacious than benzoyl peroxide/erythromycin. Dry skin was the most frequent adverse event with all three therapies.

clindamycin/benzoyl peroxide (BenzaClin, Duac), benzoyl peroxide, and clindamycin

In a ten-week, multicenter, double-blind trial, 480 patients with moderate to moderately severe acne were randomized to receive twice daily treatment with benzoyl peroxide 5% plus clindamycin 1%, benzoyl peroxide 5%, clindamycin 1%, or vehicle.[258] Significantly greater reductions in the number of inflammatory and total lesions were demonstrated in patients using combination therapy compared with those using any of the individual components. Both physicians' and patients' global evaluations showed significantly greater improvements with the combination therapy than with individual components. Dry skin was the most frequent adverse event, occurring to a similar extent in the combination and benzoyl peroxide treatment groups.

A topical gel combining benzoyl peroxide 5% and clindamycin 1% was evaluated in a ten-week, randomized, double-blind trial involving 287 patients with moderate to moderately severe acne.[259] The combination demonstrated significantly greater reductions in inflammatory lesions

than either of its components alone or vehicle. Significantly greater reductions in comedones and improvements in both physicians' and patients' global evaluations were obtained with the combination compared to clindamycin or vehicle. The reduction in comedones and the global improvements were similar between the combination and benzoyl peroxide. The incidence of dry skin in the combination group was similar to that found with benzoyl peroxide.

erythromycin and clindamycin

A 12-week, investigator-masked, randomized, parallel-group comparison of a gel formulation of erythromycin 2% with clindamycin 1% solution was performed in 102 patients with mild to moderate facial acne vulgaris.[260] Both agents were administered twice daily. Both medications significantly reduced the numbers of papules and open and closed comedones. No significant differences in lesion count reductions were detected between the treatment groups after eight and 12 weeks of treatment.

tazarotene (Tazorac), benzoyl peroxide, erythromycin/benzoyl peroxide (Benzamycin Pak), and clindamycin

A multicenter, investigator-masked, randomized, parallel-group study was performed in 440 patients with mild to moderate facial acne vulgaris to compare the efficacy and tolerability of tazarotene monotherapy with three combination regimens.[261] Patients received tazarotene plus benzoyl peroxide gel, tazarotene plus erythromycin/benzoyl peroxide gel, or tazarotene plus clindamycin phosphate lotion. The only combination therapy to achieve a significantly greater global improvement than tazarotene monotherapy was tazarotene plus clindamycin. For reducing noninflammatory lesions specifically, none of the combination regimens offered significant benefit over tazarotene monotherapy. For reducing inflammatory lesions, tazarotene plus erythromycin/benzoyl peroxide was significantly more efficacious than all the other regimens. Tazarotene plus clindamycin and tazarotene plus benzoyl peroxide reduced the incidence of adverse effects compared with tazarotene monotherapy; however, the difference was not statistically significant.

tazarotene (Tazorac) and tretinoin and clindamycin

A randomized, investigator-blinded, parallel group, multicenter study compared tazarotene 0.1% cream plus clindamycin 1% gel to tretinoin 0.025% gel plus clindamycin 1% gel in 150 patients with facial acne vulgaris.[262] At 12 weeks, the reduction in lesion counts was greater for tazarotene/clindamycin versus tretinoin/clindamycin for both the non-inflammatory lesion count (71 percent versus 52 percent, $p \leq 0.01$) and the inflammatory lesion count (77 percent versus 67 percent, $p=0.053$). More patients achieved ≥50 percent global improvement and ≥75 percent global improvement with tazarotene/clindamycin than with tretinoin/clindamycin (88 percent versus 75 percent, $p \leq 0.05$ and 66 percent versus 52 percent $p=0.10$, respectively) at week 12. Both regimens were generally well tolerated. This study was supported through a grant from Allergan.

tazarotene (Tazorac) and tretinoin

The efficacy and tolerability of tazarotene 0.1% gel and tretinoin 0.1% microsphere gel were evaluated in a multicenter, double-blind, randomized, parallel-group study in 169 patients with mild to moderate inflammatory facial acne vulgaris for 12 weeks.[263] Both agents were associated with significant reductions from baseline in the non-inflammatory and inflammatory lesion counts. Tazarotene treatment was associated with a significantly greater incidence of treatment success (defined as ≥50 percent global improvement [67 percent versus 49 percent; $p=0.03$]) and significantly greater reductions in overall disease severity (36 percent versus 26 percent; $p=0.02$) and non-inflammatory lesion count (60 percent versus 38 percent at week 12;

p=0.02) than tretinoin microsponge treatment. Both drugs were well tolerated.

A multicenter, double-blind, randomized, parallel-group study that compared the efficacy and tolerability of tazarotene and tretinoin was performed in 143 patients with mild to moderate facial acne vulgaris.[264] Patients were randomized to receive tazarotene 0.1% gel or tretinoin 0.025% gel once daily for 12 weeks. Tazarotene 0.1% gel was more effective than tretinoin 0.025% gel in reducing the open comedone count ($p \leq 0.05$) and the total non-inflammatory lesion count ($p \leq 0.05$). The total inflammatory lesion count was similar (p=NS). At some time points, tazarotene was associated with increased irritation, but peeling, erythema, dryness, burning, and itching never exceeded trace levels.

A 12-week, investigator-blinded, randomized, parallel-design trial compared the safety and efficacy of tretinoin microsphere gel 0.04% to tazarotene cream 0.05% in mild to moderate facial acne vulgaris.[265] Efficacy measurements included IGA, lesion counts, and subject self-assessment of acne signs and symptoms. Efficacy was generally comparable between treatment groups, although tretinoin provided more rapid results in several parameters. IGA showed a more rapid mean change from baseline at Week 4 in the tretinoin group (-0.18 versus -0.05 in the tazarotene group). Tretinoin improved papules more rapidly. At Week 4, the mean percentage change from baseline in open comedones was statistically significant at -64 percent in the tretinoin group (p=0.0039, within group) versus -19 percent in the tazarotene group (not statistically significant within the group; p=0.1875). Beginning with Week 4, skin dryness, peeling, and pruritus were significantly lower in the tretinoin group. Both groups had a low incidence of adverse events.

Summary

Professional guidelines recommend topical therapy as standard of care in acne treatment. The AAD guidelines recommend topical retinoids, benzoyl peroxide, and benzoyl peroxide in combination with either erythromycin or clindamycin as effective acne treatments. The Global Alliance to Improve Outcomes in Acne recommend the topical retinoids as the foundation of treatment in all patients with acne except those with the most severe disease There is no consensus about the relative efficacy of currently available topical retinoids. The concentration and/or vehicle of any particular retinoid may impact tolerability. Combination of a retinoid and antimicrobial such as benzoyl peroxide is the preferred approach for most patients with acne. This combination enhances efficacy and speed of clearing, as the agents target multiple pathophysiological factors and demonstrate broader disease effectiveness. Retinoid monotherapy or combination therapy with benzoyl peroxide should be continued as maintenance treatment due to the potential for bacterial resistance. Combination therapy of topical antibiotics and either benzoyl peroxide or topical retinoids is more effective than either agent used alone.

Benzoyl peroxide has bactericidal, keratolytic, and comedolytic activity. It has been useful as a single agent and in combination with antibiotics or retinoids for acne. Combination therapy of benzoyl peroxide with clindamycin or erythromycin is more effective than either of the individual components alone. There are many different strengths and formulations available for benzoyl peroxide. It is unknown if there is increased efficacy from higher or lower concentrations of the products, but the incidence of adverse effects may increase with greater concentrations of drug.

Azelaic acid is an effective agent that possesses comedolytic and antibacterial properties, but the comparative data for efficacy are limited. The combination of sulfur and sodium sulfacetamide is another available agent, but there are limited data regarding its efficacy.

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