Fixed-Combination Products in the Management of Acne Vulgaris

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Acne vulgaris is the most common dermatologic disorder in the United States. Although its cause is unknown, various factors are implicated in its pathogenesis. No single topical antiacne medication acts on all the major pathophysiologic events. Combined use of agents with different modes of action provides better patient outcomes than monotherapy. Topical fixed-combination therapies include antibiotics with benzoyl peroxide (BPO) or retinoids, and retinoids with BPO.

With increased efficacy can come increased irritation from the combination or formulation excipients. Surfactants, preservatives, and high levels of organic solvents including alcohols found in some products are potential irritants. This review considers data on topical fixed-combination acne medications and developments focused on newer lower concentration, optimized formulations aimed at reducing dryness and irritation without compromising efficacy. In the absence of direct comparative clinical trials, this review provides timely guidance for clinicians on the use of these agents.

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Acne vulgaris is the most common dermatologic disorder in the United States. At least 4 pathophysiologic events take place, including androgen-mediated stimulation of sebaceous gland activity, abnormal keratinization leading to follicular plugging, proliferation of *Propionibacterium acnes* within the hair follicle, and inflammation.[1,2] Genetic factors,[3] stress,[4] and possibly diet may influence the condition's development and severity.[5]

In mild to moderate disease, topical agents are successfully used in fixed combination without addition of an oral agent. Multiple deeper inflammatory and nodular acne lesions dominate in more severe cases, warranting more aggressive treatment with oral agents from the outset.[6-10]

Antibiotics, antimicrobials, and retinoids can reduce acne lesion counts and inflammation; antibiotics and antimicrobials can reduce *P acnes* counts. No single agent effectively targets all of the pathophysiologic components of acne. Targeting each of the factors that aggravate acne, combination therapy has become the standard of care and provides better patient outcomes.[11,12] Combination therapy often is more convenient and has the potential to improve adherence.[13] Fixed-combination products demonstrate significantly greater and faster results than individual active ingredients in clinical trials.[14-16] A number of fixed-combination products are approved by the US Food and Drug Administration and are available in the United States.

With increased efficacy can come increased irritation. Benzoyl peroxide (BPO) and retinoids can cause erythema, dryness, peeling, stinging, and burning when used as monotherapy. Surfactants, preservatives, and high levels of organic solvents including alcohols are potential irritants.[11,17]

This review will consider topical fixed-combination acne medications and developments focused on newer lower concentration, optimized formulations

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aimed at reducing dryness and irritation without compromising efficacy.

Topical Antibiotic and BPO Fixed-Combination Therapies

Clinical trials have shown that twice-daily use of clindamycin 1%–BPO 5% gel for 10 to 16 weeks was more effective in reducing inflammatory lesion counts than individual active ingredients or vehicle in mild to moderately severe acne.[18,19] Benzoyl peroxide radicals, the most active form of BPO, are greatly increased when BPO is combined with chemical structures containing a tertiary amine (eg, clindamycin, erythromycin).[20] The combination is rapidly bactericidal and reduces development of antibiotic-resistant bacteria.[21,22] Combination therapy also may improve tolerability.[23] When available, a once-daily regimen may enhance compliance.[24]

Studies with erythromycin 3%–BPO 5% fixed combination suggest the addition of BPO prevents development of resistant *P acnes* strains.[25,26] Twice-daily use of erythromycin 3%–BPO 5% gel was compared with erythromycin 4%–tretinoin 0.025% gel in moderate acne. Significantly greater improvements in global physician rating ($P=.022$) and aggregate scores of physician-rated ($P=.008$) and participant-rated ($P=.004$) severity were reported with the fixed combination of erythromycin 3%–BPO 5% at week 12.[27]

In a randomized controlled trial, 334 participants were treated once nightly with a fixed combination of clindamycin 1%–BPO 5% gel, BPO 5%, clindamycin 1%, or vehicle.[15] After 11 weeks, 66% of participants receiving clindamycin-BPO experienced good or excellent responses compared with 41% receiving BPO 5% and 36% receiving clindamycin 1% (all $P\leq.01$ vs vehicle). Fixed-combination therapy was superior to individual active ingredients and vehicle in reducing inflammatory lesion counts, and it was superior to vehicle and clindamycin in reducing noninflammatory lesion counts. Participants receiving clindamycin-BPO had a 61% mean reduction in inflammatory lesion counts ($P\leq.002$ vs vehicle; $P<.02$ vs monotherapies) compared with a 39% reduction in participants receiving BPO 5% and a 35% reduction in those receiving clindamycin 1% (both $P\leq.002$ vs vehicle)(Figure 1). The mean reduction in noninflammatory lesion counts was 36% with clindamycin-BPO compared with 30% with BPO 5% and 9% with clindamycin 1% (both $P<.02$ vs vehicle).[15] These data suggest that most of the treatment-related comedolytic effect was due to BPO.

All treatments were well-tolerated. Peeling was worse in the clindamycin-BPO treatment group and erythema was worse in the BPO 5% treatment group, perhaps attributable to the anti-inflammatory effect of clindamycin.[15]

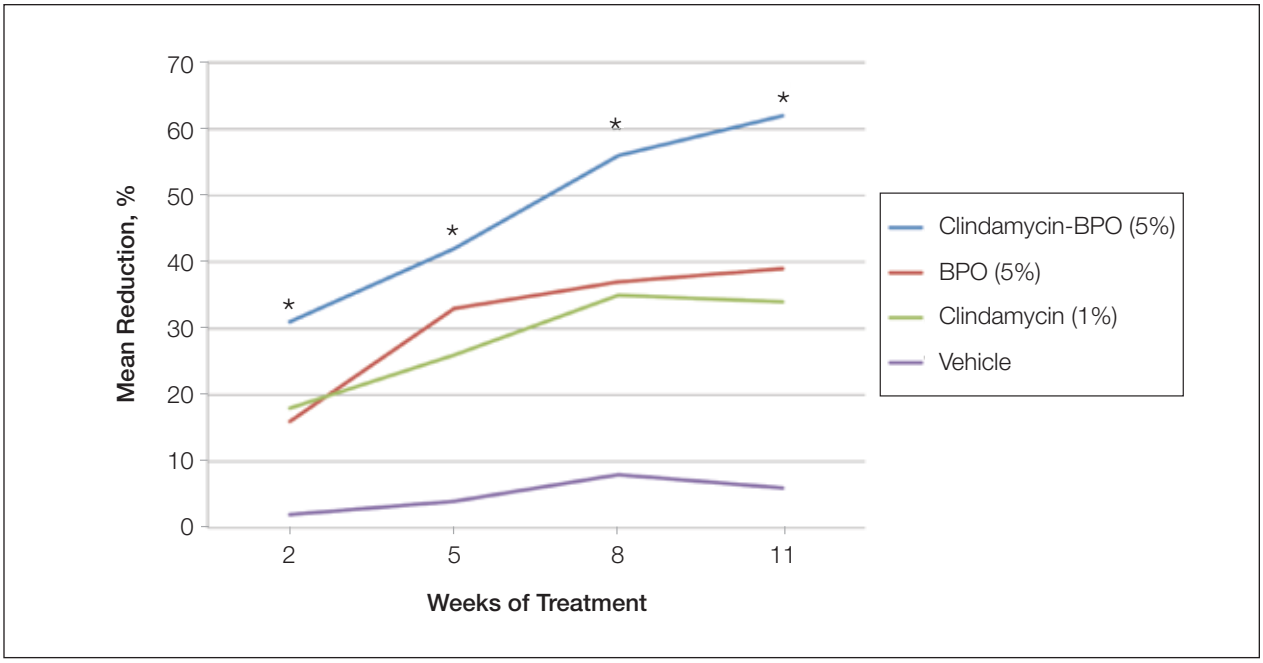

Figure 1. Mean percentage reduction in inflammatory lesion counts over study period in participants treated with clindamycin 1%–benzoyl peroxide (BPO) 5% gel compared with active ingredients (BPO 5% and clindamycin 1%) and vehicle. Asterisk indicates $P\leq.002$ vs vehicle for all treatments, and $P<.02$ vs BPO (at weeks 2, 8, and 11) and clindamycin (at weeks 2, 5, 8, and 11). Reprinted from *J Am Acad Dermatol,* ©1997, with permission from the American Academy of Dermatology.[15]

A 16-week trial in 79 participants demonstrated a 53% mean lesion count reduction with twice-daily use of a fixed combination of clindamycin phosphate 1%–BPO 5% gel and 28% with clindamycin phosphate 1% alone ($P=.013$). By week 8, the mean percentage reductions in both inflammatory and noninflammatory lesion counts were significantly greater with combination therapy versus monotherapy ($P=.014$ and $P=.018$, respectively).[16]

A review of 3 independent clinical trials in 1259 participants concluded that a fixed combination of clindamycin 1%–BPO 5% gel was more effective than individual active ingredients in reducing inflammatory and noninflammatory lesion counts and suppressing *P acnes*.[28] Its antimicrobial activity was significantly superior to individual active ingredients (each $P<.01$) and numerically better than erythromycin 3%–BPO 5%. Facial skin dryness was the most frequent side effect, with isolated incidences of localized irritation.[28]

Another study comparing twice-daily use of a fixed combination of clindamycin phosphate 1%–BPO 5% gel, clindamycin phosphate 1%, and vehicle in healthy volunteers with high levels of facial *P acnes* found the fixed-combination gel markedly reduced *P acnes* colony counts.[29] Clindamycin-BPO produced 91% inhibition of *P acnes* levels from baseline following 24 hours of application ($P<.001$ vs vehicle). By the end of the 2-week study, the fixed-combination gel had produced 99.9% inhibition.[29]

In 2008 a once daily, fixed combination of clindamycin phosphate 1.2% and low-concentration BPO 2.5% was approved by the US Food and Drug Administration for the treatment of acne vulgaris in patients 12 years or older.

Topical Retinoid and Antibiotic Fixed-Combination Therapies

Topical retinoids (eg, tretinoin, adapalene) in combination with topical antibiotics (eg, clindamycin, erythromycin) have been shown to be more effective than monotherapy in mild to moderate acne.[30-33]

Fixed-combination clindamycin 1%–tretinoin 0.025% gel was compared with individual active ingredients in 64 participants. After 8 weeks, the fixed-combination product showed numerical improvement in both comedone and inflammatory lesion counts compared with tretinoin alone and greater improvement compared with clindamycin alone.[33] The fixed-combination product was better tolerated than tretinoin,[33] possibly because clindamycin is believed to decrease the irritant effects of tretinoin.[32]

A clinical trial in 249 participants with mild to moderate acne vulgaris showed that treatment with clindamycin phosphate lotion 1% and adapalene gel 0.1% was significantly more effective than clindamycin lotion after 12 weeks, with a greater reduction in total ($P<.001$), inflammatory ($P=.004$), and noninflammatory ($P<.001$) acne lesion counts. A significantly greater and faster efficacy response was seen with no significant tolerability concerns.[30] Other trials have shown similar results.[30,31,34,35]

A 14-week, open-label, multicenter trial in 1324 participants from a general practice confirmed the good efficacy and tolerability profile of fixed-combination preparations containing tretinoin 0.025% and erythromycin 4%, but no direct comparisons were made with the individual ingredients.[35]

Topical Retinoid and BPO Fixed-Combination Therapies

Fixed-combination therapy with topical retinoids and BPO follows the same underlying principles—using 2 products in fixed combination that have complementary modes of action—but without the potential for antibiotic resistance. The efficacy of topical vitamin A and BPO has been shown in an open-label trial of 404 participants with moderate to severe acne. Eighty-eight percent of participants receiving the fixed-combination therapy achieved 80% to 90% clearing of acne lesions after 6 to 8 weeks.[36]

The primary limitation of BPO is concentration-dependent irritation and stratum corneum dryness. High concentrations of BPO (≥5%) can result in skin irritation and may impact patient compliance, thereby limiting its use.[37,38] A 21-day cumulative irritancy study showed that adapalene can be coadministered with BPO, clindamycin, and erythromycin with little or no evidence of irritancy.[39]

In 2009 a fixed combination of a retinoid (adapalene 0.1%) and low-concentration BPO 2.5% was approved for the treatment of acne vulgaris in patients 12 years and older. A 12-week randomized trial comparing adapalene 0.1%–BPO 2.5% gel with adapalene 0.1% or BPO 2.5% in 517 participants found the fixed-combination product was significantly more effective than the monotherapies ($P<.001$), with significant differences in total lesion counts as early as week 1 ($P=.001$ vs adapalene; $P=.01$ vs BPO; $P=.002$ vs vehicle).[40] Most participants (96%) had mild to moderate acne. Median reduction in inflammatory lesion counts with adapalene-BPO at week 12 was 63% compared with 46%, 44%, and 38% with adapalene 0.1%, BPO 2.5%, and vehicle, respectively. Median reduction in noninflammatory lesion counts with adapalene-BPO at week 12 was 51% compared with 33%, 36%, and 38%, respectively (Table).[40]

Relative success rates (clear, almost clear) are shown in Figure 2. The adapalene-BPO fixed

Primary Efficacy Parameters: Adapalene 0.1%–BPO 2.5% Gel Compared With Active Ingredients and Vehicle (N=517)

	Treatment Group				*P* Value		
	Adapalene 0.1%–BPO 2.5% (n=149) (Group 1)	Adapalene 0.1% (n=148) (Group 2)	BPO 2.5% (n=149) (Group 3)	Vehicle (n=71) (Group 4)	Group 1 vs Group 2	Group 1 vs Group 3	Group 1 vs Group 4
Success rate, %	27.5	15.5	15.4	9.9	.008	.003	.002
Median reduction in lesion count at week 12, %							
Total lesions	51.0	35.4	35.6	31.0	<.001	<.001	<.001
Inflammatory lesions	62.9	45.7	43.6	37.8	<.001	<.001	<.001
Noninflammatory lesions	51.2	33.3	36.4	37.5	<.001	<.001	<.001

Abbreviation: BPO, benzoyl peroxide.

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combination (28%) was superior to adapalene 0.1% (16%; *P*=.008), BPO 2.5% (15%; *P*=.003), and vehicle (10%; *P*=.002) at study end point (week 12).[40]

In a 12-month, open-label, continuous-use trial of adapalene 0.1%–BPO 2.5% gel in 452 participants, early and sustained reductions in inflammatory and noninflammatory lesion counts were observed and were clinically significant from week 1.[41] The median percentage reduction in inflammatory, noninflammatory, and total lesion counts at study end point was 76%, 70%, and 71%, respectively. Adverse events were mild to moderate in severity, most occurring during the first 3 months of the study (104/452 [23%]). The most common treatment-related adverse event was dry skin (17%).[41]

In one trial, 60 participants were randomized to fixed-combination adapalene 0.1%–BPO 2.5% gel versus BPO 2.5% or BPO 5% monotherapy, or adapalene 0.1%–BPO 5% gel versus BPO 5% or BPO 10% monotherapy. The cutaneous tolerability profile was best with adapalene 0.1%–BPO 2.5%, which was similar to BPO 2.5% or BPO 5% monotherapy.[42]

Fixed-Combination Therapy in the Future: Efficacy, Tolerability, and Choices

Combining agents has become the standard of care for acne. With the increasing emergence of antibiotic resistance to *P acnes*, BPO is considered an important component, as it reduces the development and emergence of antibiotic-resistant strains.[43,44]

What is the best combination to use? Direct comparisons regarding efficacy and tolerability are not available. Patient compliance, convenience, and other factors such as improvement in quality of life become important considerations.

The main reason for treatment failure in acne is poor compliance.[45] Noncompliance can be as high as 52% after 3 months.[46] Compliance generally is considered to be a function of efficacy, rapidity of results, patient understanding of the regimen, simplicity and convenience of the regimen, and tolerability.[24,47] Compliance is better with regimens that involve fewer agents and less frequent dosing.[24,48-50] A study in 105 participants compared compliance rates for 6 consecutive months of once-daily, twice-daily, and thrice-daily dosing regimens. Eighty-four percent of participants were compliant with once-daily dosing compared with 75% and 59% with twice-daily and thrice-daily dosing, respectively.[48]

Tolerability can be influenced by active ingredients and vehicle formulation. Benzoyl peroxide and retinoids may alter the epidermal barrier and cause erythema, dryness, peeling, stinging, and burning. Surfactants, preservatives, and high levels of organic solvents including alcohols, which

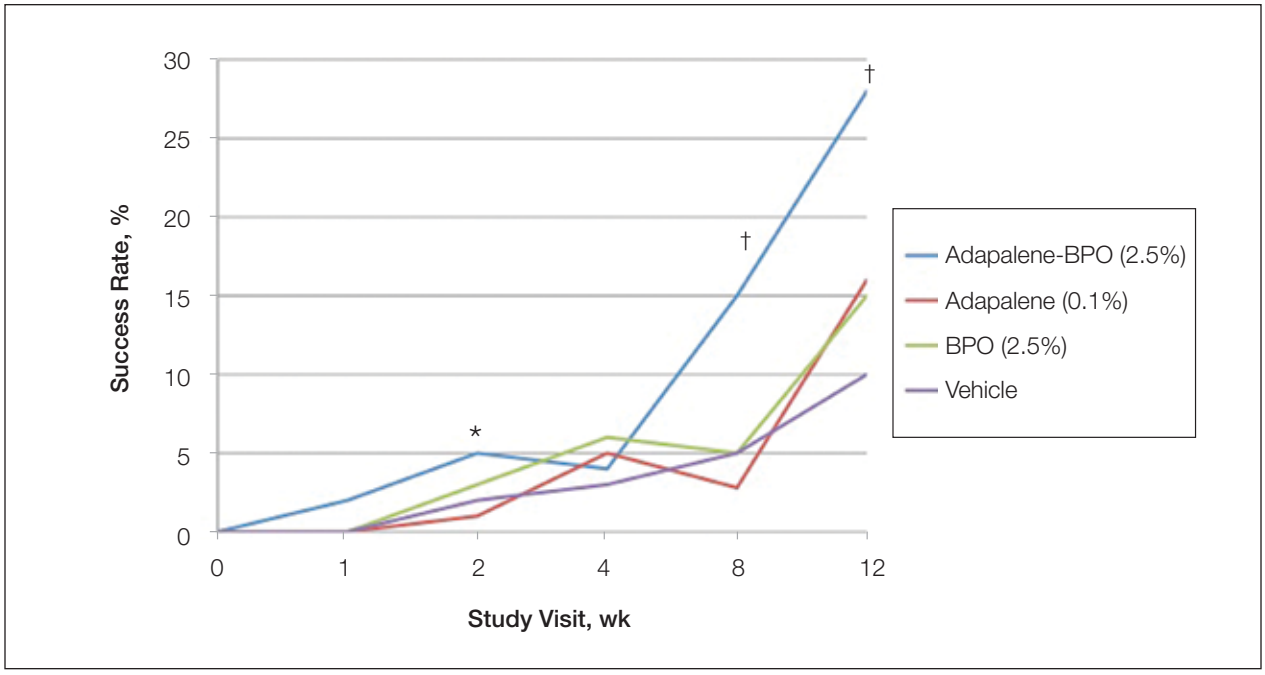

Figure 2. Relative success rates (clear, almost clear) during the course of the study. Treatment with adapalene 0.1%–benzoyl peroxide (BPO) 2.5% gel was compared with active ingredients (adapalene 0.1% and BPO 2.5%) and vehicle. Asterisk indicates $P=.042$ (adapalene-BPO vs adapalene); dagger, $P<.05$ (adapalene-BPO vs all other treatments). Reprinted from *J Am Acad Dermatol*, ©2007, with permission from the American Academy of Dermatology.[40]

are often used in vehicle formulations, are potential irritants.[12,13] Interest in studies implementing various formulations has increased because vehicle excipients may improve drug delivery, alter drug concentration or bioavailability, and decrease irritation.[51,52]

An ideal fixed-combination acne product would fulfill the following criteria: once-daily application, low concentration of BPO (<5%), stability, and a vehicle that enhances BPO bioavailability while minimizing irritation.

It has been reported that a lower concentration of BPO 2.5% was as effective as higher concentrations (eg, 5%, 10%), with a low rate of frequency and severity of skin irritation and allergic reactions.[37,38] However, these studies may not have used adequate power calculations to detect a statistical difference.

A once-daily fixed-combination product with a low concentration of BPO 2.5% and clindamycin phosphate 1.2% was introduced in the United States to provide an optimized formulation with a low concentration of BPO, low potential irritancy, and high bioavailability.[52]

A 21-day cumulative irritation study of fixed-dose clindamycin-BPO formulations with varying concentrations of BPO but the same vehicle showed that there was a marked 33% reduction in mean irritancy score when the BPO concentration was reduced from 5% to 2.5%. A percutaneous skin penetration study showed that clindamycin phosphate 1.2%–BPO 2.5% achieved skin penetration comparable to clindamycin-BPO products containing BPO 5%.[52]

Clindamycin phosphate 1.2%–BPO 2.5% gel was studied for the once-daily treatment of moderate to severe acne in more than 2800 participants; approximately 19% of participants had severe acne based on the evaluator global severity scores.[53] By week 12, the median percentage reduction in inflammatory lesion counts with clindamycin-BPO was 64% compared with a 54% reduction with clindamycin phosphate 1.2%, 55% reduction with BPO 2.5%, and 34% reduction with vehicle (all $P<.001$). Median percentage reduction in noninflammatory lesion counts was 49%, 40%, 44%, and 26%, respectively, and 52%, 45%, 47%, and 27%, respectively, for total lesion counts (Figure 3).[54] Relative success (clear, almost clear at week 12) is shown in Figure 4.[53]

Cutaneous tolerability was excellent. Mean scores for erythema, scaling, itching, burning, and stinging at each postbaseline visit were less than 1 (1=mild) and comparable with active ingredients and vehicle.[53]

Conclusion

Combined use of acne therapies, particularly fixed-combination products, has become the standard of

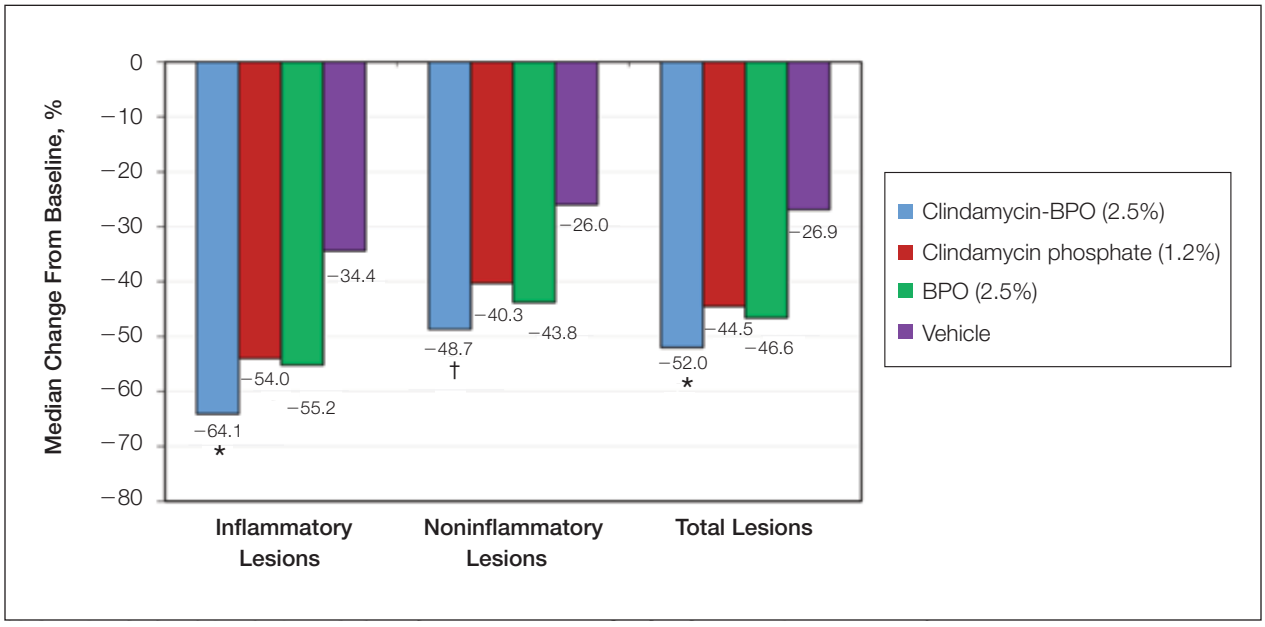

Figure 3. Median percentage reduction in inflammatory, noninflammatory, and total lesion counts from baseline to week 12. Treatment with clindamycin phosphate 1.2%–benzoyl peroxide (BPO) 2.5% gel was compared with active ingredients (clindamycin phosphate 1.2% and BPO 2.5%) and vehicle. Last observation carried forward was used to impute missing data prior to analysis. Asterisk indicates $P<.001$ (clindamycin-BPO 2.5% vs all other treatments); dagger, $P<.001$ (clindamycin-BPO 2.5% vs clindamycin phosphate 1.2% and vehicle), and $P=.001$ (clindamycin-BPO vs BPO 2.5%). Adapted from Gold.[54]

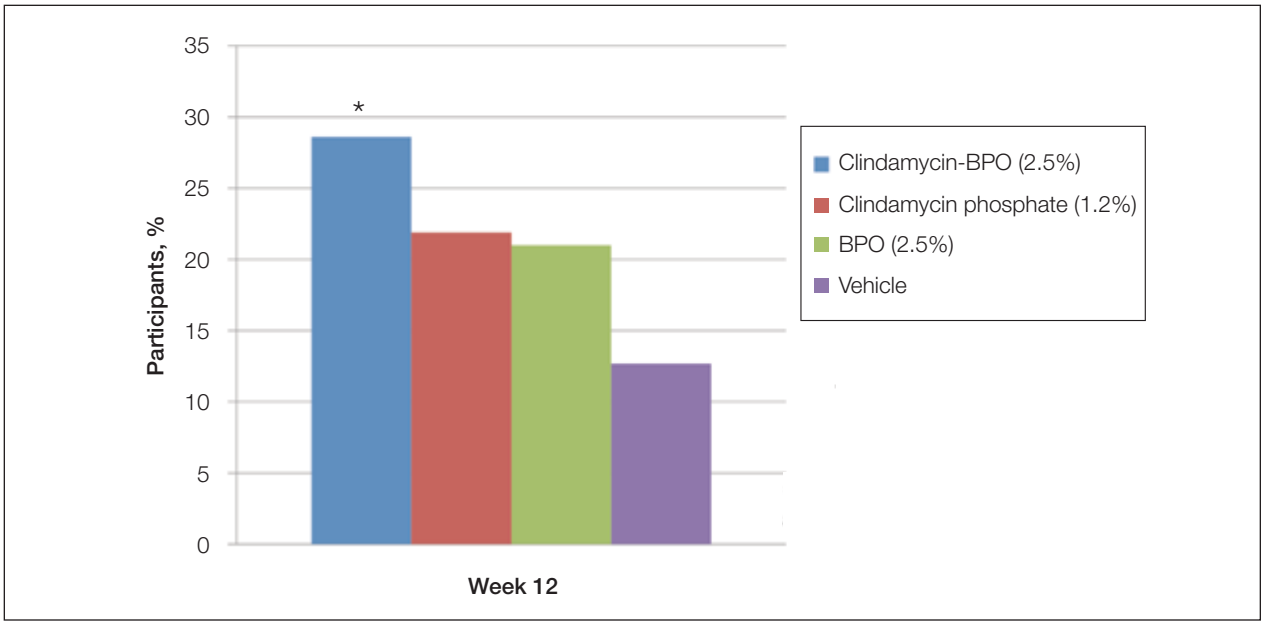

Figure 4. Investigator assessment of percentage of participants with relative success (clear, almost clear) at week 12. Treatment with clindamycin phosphate 1.2%–benzoyl peroxide (BPO) 2.5% gel was compared with active ingredients (clindamycin phosphate 1.2% and BPO 2.5%) and vehicle. Asterisk indicates $P=.001$ (clindamycin-BPO 2.5% vs clindamycin phosphate 1.2%), and $P<.001$ (clindamycin-BPO 2.5% vs BPO 2.5% and vehicle). Reprinted from *J Am Acad Dermatol*, ©2008, with permission from the American Academy of Dermatology.[53]

care and is the most effective approach. A number of fixed-combination products are now available to treat mild to moderate acne. Most therapies are centered on BPO to minimize the emergence of resistance. However, BPO can cause irritation and dryness, limiting its use in certain patients. The cutaneous tolerability of BPO has been shown to be dose dependent, and 2 once-daily fixed combinations containing a low concentration of BPO 2.5% are available. Both agents show rapid onset of action with results in the first 1 to

2 weeks of therapy. Clindamycin phosphate 1.2%–BPO 2.5% was well-tolerated throughout the study period.[53] Adapalene 0.1%–BPO 2.5% can cause mild to moderate irritation in the first 1 to 2 weeks.[40] Choice of fixed-combination product depends on a number of factors, including the patient's acne severity and prior treatments. These newer fixed combinations offer patients effective, well-tolerated solutions that should improve patient compliance and clinical outcomes.

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