# Combining Clindamycin 1%–Benzoyl Peroxide 5% Gel With Multiple Therapeutic Options

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*This article reports on recent studies and case reports that evaluated the stability, tolerability, and efficacy of clindamycin 1%–benzoyl peroxide 5% tube gel in combination with topical retinoids and oral antibiotics. Overall, these combinations appeared to be well-tolerated, effective, and, as reported in the case studies, adaptable to common clinical practice.*

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Several topical agents, including antibiotics, antimicrobials, and retinoids, are available for the treatment of acne. When used as monotherapy, these products can reduce lesion counts and inflammation as well as eradicate *Propionibacterium acnes*. Despite the efficacy profiles of individual topical agents, the use of antibiotics such as clindamycin or erythromycin in combination with benzoyl peroxide produces greater outcomes than monotherapy; additionally, combination therapy prevents the emergence of resistant *P acnes*.[1]

Investigators recently have turned their attention to antibiotic–benzoyl peroxide combinations applied concomitantly with topical retinoids, a strategy that may address the underlying pathophysiology of acne more so than monotherapy. In addition to the potential for increased efficacy, there is the potential for increased irritation; topical benzoyl peroxide and retinoids may alter the epidermal barrier and cause erythema, dryness, peeling, stinging, and burning.

We report the results of 3 studies and 2 case reports evaluating clindamycin 1%–benzoyl peroxide 5% tube gel in combination with other treatments for acne. Overall, the use of this product as part of a larger treatment regimen appeared to be well-tolerated and more efficacious than monotherapy.

## Clindamycin 1%–Benzoyl Peroxide 5% Gel in Combination With Topical Retinoids and Sunscreens

When simultaneously combining multiple topical products, compatibility and stability are concerns. Multiple-drug combinations may be rendered ineffective if one product causes another to degrade. Moreover, compatibility, or lack thereof, affects when and how products are applied. For example, if 2 products are incompatible and become unstable when applied together, different application times may be needed to maintain the therapeutic effect (eg, applying one product in the morning and the other product in the evening). Complex application schedules may adversely affect patient compliance. If 2 products can be applied sequentially,

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patients may be more likely to adhere to the dual-treatment regimen.

Del Rosso and Bikowski[2] conducted a 2-part study evaluating the chemical stability of the patented tube gel formulation of clindamycin 1%–benzoyl peroxide 5% when applied with each topical retinoid (adapalene gel 0.1%, tretinoin gel microsphere 0.1%, and tazarotene cream 0.1%) and sunscreens containing avobenzone, octinoxate, oxybenzone, octisalate, and homosalate. In the second part of the study, the tolerability of each of the combinations was evaluated.[2]

*Stability*—To test chemical stability, clindamycin 1%–benzoyl peroxide 5% was admixed in equal amounts by weight with the 3 topical retinoids and sunscreen.[2] Each mixture of 2 products was held at 35°C. High performance liquid chromatography was performed at baseline (immediately after mixing) and at 1, 2, 4, 6, and 24 hours. Stability results were reported as the percentage of the theoretical concentration (actual measurement at time point/baseline-stated concentration) at each time point.[2]

When combined, adapalene, benzoyl peroxide, and clindamycin all remained stable at each time point up to 24 hours.[2] None of the products appeared to degrade. At 24 hours, the concentrations were 106%, 104%, and 102%, respectively.[2]

Tretinoin gel microsphere 0.01% demonstrated a progressive decline in concentration over time; however, tretinoin remained stable at 6 hours.[2] At baseline, it was 96% stable. Stability decreased to 92% by 2 hours, 84% by 6 hours, and 56% by 24 hours.[2]

Stability results with tazarotene cream 0.1% were indeterminate because tazarotenic acid, the active metabolite, was not measured.[2] The study methodology did not account for how rapidly tazarotene is converted to tazarotenic acid in the skin.[3,4] An assay procedure evaluating tazarotenic acid levels is needed to fully assess stability.[2]

Twenty-four hour stability data also indicated that benzoyl peroxide and clindamycin retained its chemical stability when applied with each of the sunscreens. The sunscreens also remained stable.[2]

*Tolerability*—The second phase of this study was an investigator-blinded, randomized, split-face trial evaluating the tolerability of the combinations in 18 subjects (12 women, 6 men), aged 18 to 26 years (mean age, 22 years), with mild or moderate acne vulgaris.[2] The subjects applied clindamycin 1%–benzoyl peroxide 5% tube gel to one side of the face, as well as adapalene gel 0.1%, tazarotene cream 0.1%, or tretinoin gel microsphere 0.04% (n=6 in each group) and a moisturizer sunscreen. On the other side of the face, the same topical retinoid plus a moisturizer sunscreen was applied. Investigators scored tolerability in terms of erythema, dryness, and peeling using a 5-point scale (0=absent and 4=severe). Subject evaluations of erythema, dryness, pruritus, and burning were scored using a 4-point scale (0=none and 3=very red, very dry, or severe/strong).[2]

Overall, the combination of clindamycin 1%–benzoyl peroxide 5% plus a retinoid appeared to be well-tolerated.[2] Most subjects experienced mild to moderate local reactions (ie, erythema, dryness, peeling, pruritus, or burning); however, a study comprised of a larger sample size is necessary to make definitive conclusions on the tolerability and efficacy of this treatment option.[2]

## Clindamycin 1%–Benzoyl Peroxide 5% Gel in Combination With Tretinoin Cream 0.025%

Single-product combinations of clindamycin 1%–benzoyl peroxide 5% gel are available in 2 formulations: (1) a ready-to-use tube gel containing glycerin, a humectant, and dimethicone, an emollient with occlusive properties, and (2) a jar gel that does not contain these excipients and requires compounding by the pharmacist before dispensing. Glycerin and dimethicone assist in retaining epidermal moisture, which may limit irritation, particularly when applied with a topical retinoid. The tube gel is approved by the US Food and Drug Administration for once-daily application to treat inflammatory acne vulgaris, whereas the jar gel is approved for twice-daily application to treat acne vulgaris. In addition, the tube gel may enhance tolerability to topical retinoids, making it preferable to patients and increasing compliance. Draelos and colleagues[5] conducted a split-face randomized study comparing the tolerability of the tube gel and jar gel formulations of clindamycin 1%–benzoyl peroxide 5% in combination with tretinoin cream 0.025%. The researchers also assessed the cosmetic attributes and packaging of the 2 gels. Forty-six women (mean age, 32 years) were enrolled.[5]

Forty-three (94%) subjects completed the study.[5] Subjects were required to have a minimum of 8 and a maximum of 100 inflammatory lesions (papules and pustules), a minimum of 8 noninflammatory lesions (open and closed comedones), and no more than one facial nodulocystic lesion. After a 14-day washout period for topical acne medications and a 30-day washout period for systemic acne treatments, systemic corticosteroids, or systemic antibacterials, all subjects applied the tretinoin to the entire face

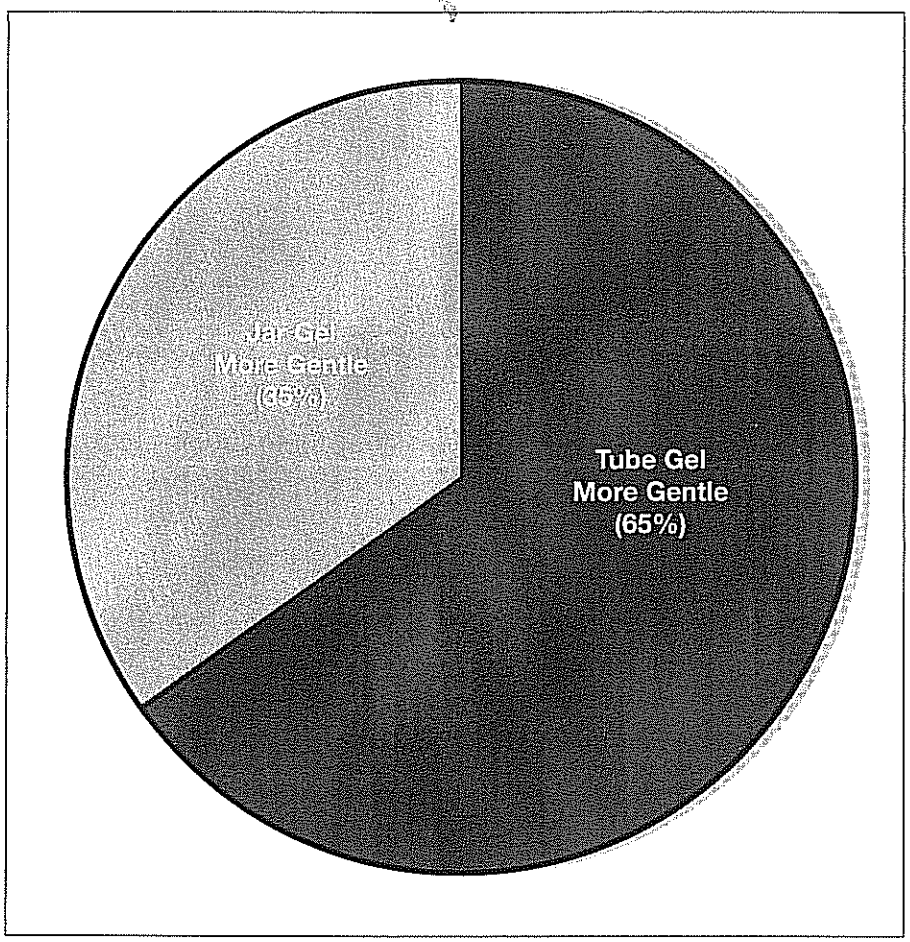


**Figure 1.** The tube gel formulation of clindamycin 1%–benzoyl peroxide 5% was gentler to the skin than the jar gel.[5]

nightly. In the morning, clindamycin 1%–benzoyl peroxide 5% tube gel was applied once daily to one side of the face. The jar gel was applied twice daily to the other side of the face (60 minutes after tretinoin cream 0.025%).[5]

Skin sensitivity and acne severity were evaluated at baseline.[5] Tolerability was graded for erythema, dryness, and peeling by investigators at baseline and days 4, 7, and 14 using a 5-point scale (0=absent and 4=severe). Subject assessments of erythema, dryness, pruritus, or burning were conducted at days 4, 7, and 14 using a 4-point scale (0=none and 3=very red, very dry, or strong).[5]

Investigator assessments revealed that the tube gel was associated with significantly less erythema, dryness, and peeling at days 4 and 7 ($P<.05$) versus the jar gel.[5] At day 14, there continued to be significantly less erythema and dryness with the tube gel ($P<.05$) versus the jar gel. Subjects reported significantly less burning at day 4 ($P<.05$) versus the jar gel. There were no subject-assessed differences in erythema or pruritus.[5]

To assess subject preference, study participants completed questionnaires at baseline and day 4 about product packaging, cosmetic acceptability, and product preference.[5] Results indicated that there were no significant differences between the tube gel and jar gel for pleasantness of smell, greasiness, ease of spreading, sticky feel, and tightness of face after application. However, significantly more subjects found the tube gel easier to use (33 subjects [72%] vs 13 subjects [28%], respectively; $P<.05$) and less messy to use (30 subjects [65%] vs 16 subjects [35%], respectively; $P<.05$). Significantly more subjects found the tube gel was gentler to the skin ($P<.05$)(Figure 1). Twenty-five subjects (54%) indicated that they preferred the tube gel overall versus the jar gel.[5]

Although both formulations were well-tolerated, the tube gel was associated with less erythema, dryness, and peeling than the jar gel when applied concomitantly with tretinoin. Subjects also found that the tube gel was gentler to the skin and easier to apply, and subjects generally preferred the tube gel.[5]

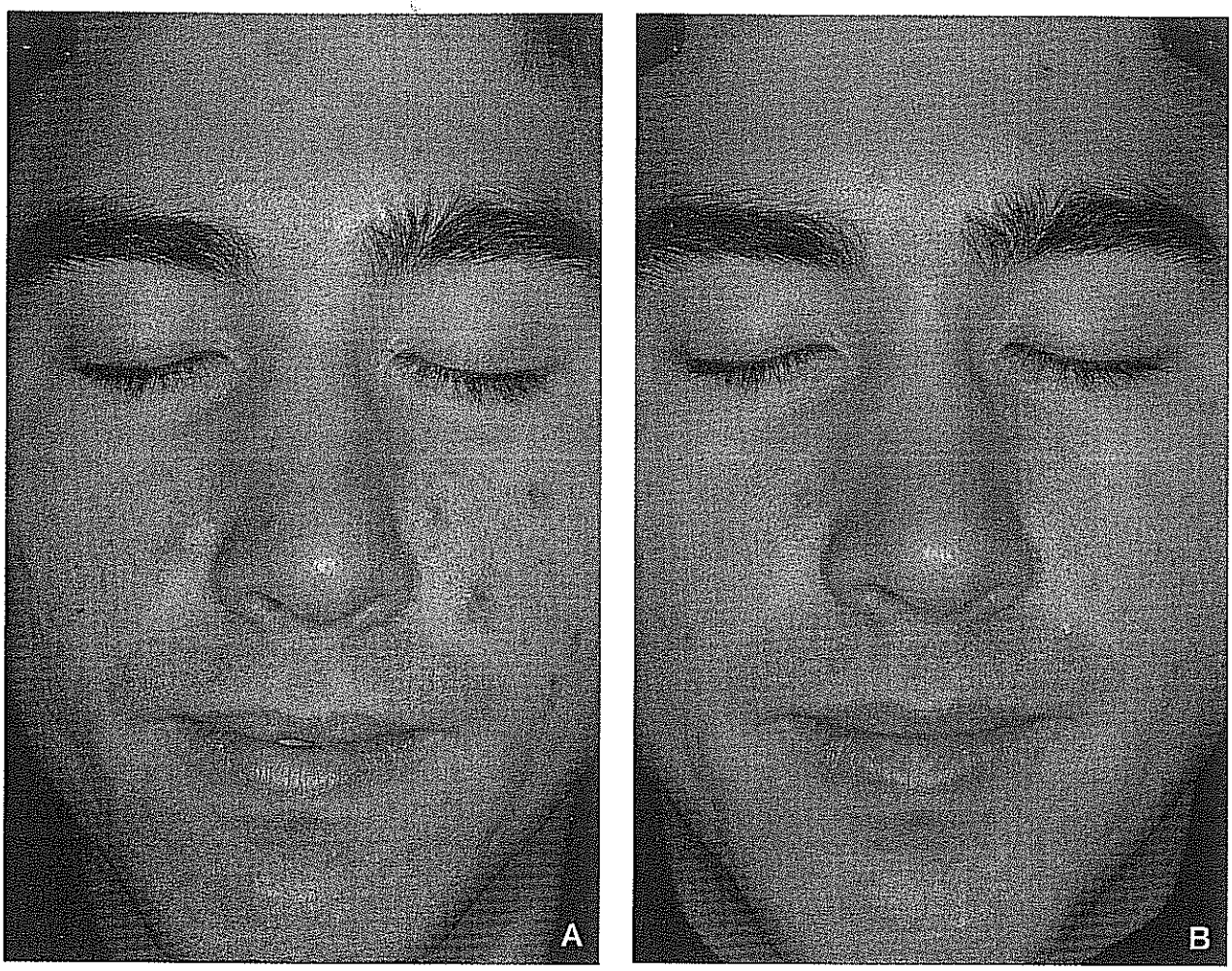


**Figure 2.** Patient with severe acne vulgaris before (A) and after (B) treatment with clindamycin 1%–benzoyl peroxide 5% gel, tazarotene cream 0.1%, and oral minocycline hydrochloride.[6]

## Clindamycin 1%–Benzoyl Peroxide 5% Gel in Combination With Tazarotene Cream 0.1% and Oral Minocycline Hydrochloride

Tanghetti[6] evaluated a 4-drug combination for the treatment of severe acne vulgaris. The open-label study enrolled 14 subjects (7 males and 7 females) with at least 30 facial inflammatory lesions (papules and pustules); at least 10 facial noninflammatory lesions (open or closed comedones); no more than 10 facial inflammatory lesions larger than 5 mm in diameter; and a few inflammatory lesions that were suppurative and/or hemorrhagic. All subjects were at least 12 years old (mean age, 16.5 years) with severe facial acne vulgaris unresponsive to systemic antibiotics used alone.[6]

Subjects applied clindamycin 1%–benzoyl peroxide 5% tube gel in the morning and tazarotene cream 0.1% in the evening.[6] Oral minocycline hydrochloride 100-mg capsules were administered twice daily. The primary efficacy measure was the investigator's assessment of global response to treatment. Secondary efficacy measures included inflammatory and noninflammatory lesion counts and nodule/cyst count as well as overall disease severity. Investigator grading of erythema, dryness, peeling, and perception of oiliness, and subject grading of pruritus and burning also were secondary efficacy variables. Treatment lasted for 12 weeks, with follow-up examinations at baseline and weeks 4, 8, and 12.[6]

Twelve of 14 subjects completed the study.[6] At the 12-week follow-up examination, the 4-drug combination produced statistically significant mean percentage reductions from baseline in the inflammatory lesion count (72% reduction; $P<.0001$) and the noninflammatory lesion count (65% reduction;

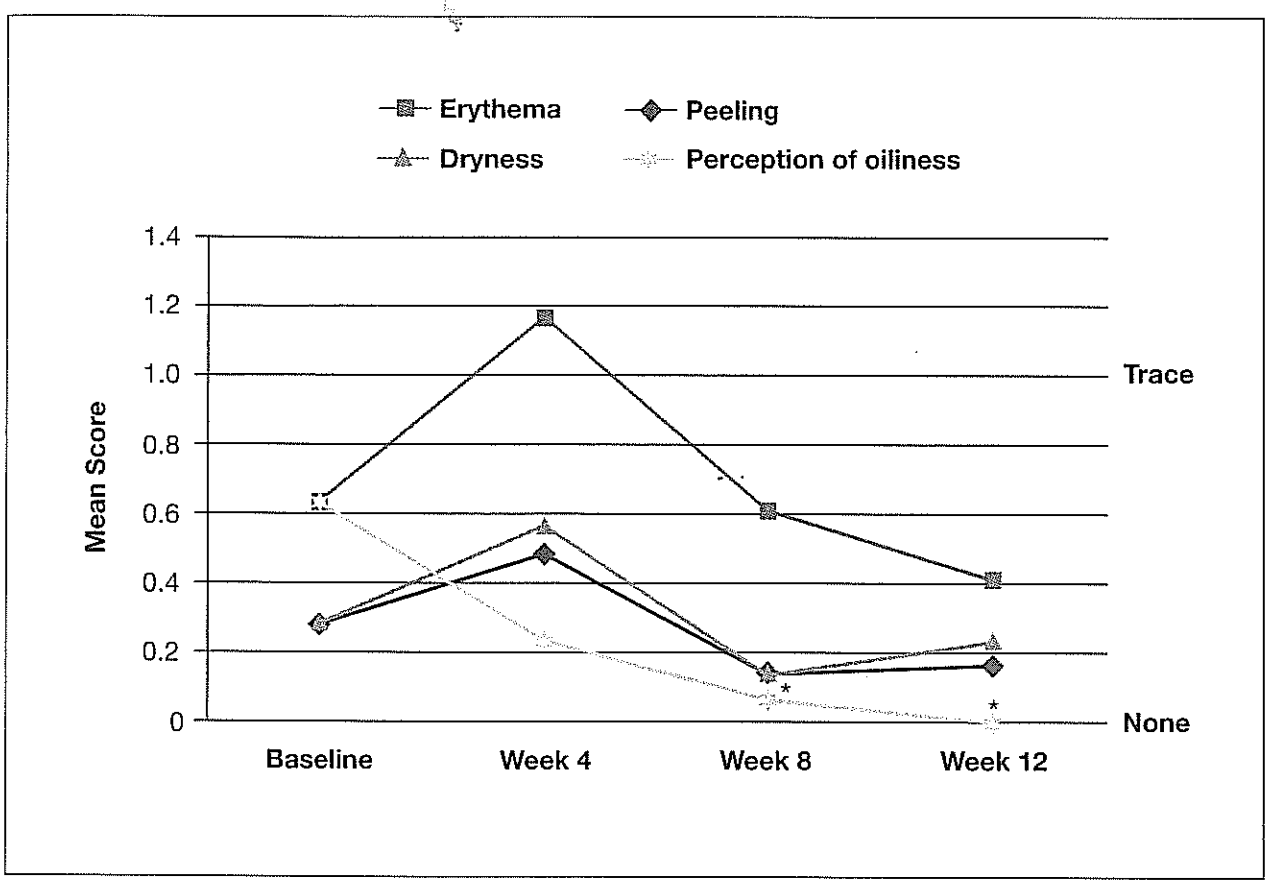


**Figure 3.** Investigator grading of erythema, dryness, peeling, and perception of oiliness over 12 weeks of treatment. Asterisk indicates significant change from baseline ($P<.05$).[6]

$P<.0001$) as well as a 95% reduction in the nodule/cyst count ($P<.01$). After 12 weeks of treatment, 8 subjects (67%) qualified as responders (at least marked improvement) for global response to treatment, and there was a significant improvement ($P<.01$) in overall disease severity at weeks 8 and 12 compared to baseline (Figure 2). Importantly, tolerability was considered acceptable by both physicians and subjects. Investigator grading of erythema, dryness, peeling, and perception of oiliness over 12 weeks of treatment is shown in Figure 3.[6]

The combination approach reported here may constitute an effective and well-tolerated alternative in patients with severe acne vulgaris.

## Case Reports

Several case reports illustrate the use of various combinations of clindamycin 1%–benzoyl peroxide 5% gel in clinical practice and the results achieved with these combinations.

*Patient 1*—A 16-year-old Asian adolescent girl presented with a 6-month history of multiple inflammatory papules and pustules and open and closed comedones on the forehead, cheeks, chin, and malar eminences (Figure 4A).[7] Prior treatment consisted of over-the-counter products. She was prescribed a combination of clindamycin 1%–benzoyl peroxide 5% gel to be applied to the entire face at night, along with a gentle cleanser and noncomedogenic moisturizer for twice-daily use. After 8 weeks of treatment, tazarotene cream 0.1% was added to the regimen for nightly application after clindamycin 1%–benzoyl peroxide 5% gel.[7]

After 4 weeks of treatment, there was at least a 75% reduction of inflammatory papules and pustules across the patient's forehead, cheeks, chin, and nose (Figure 4B).[7] At 8-week follow-up, there was at least a 95% reduction of all inflammatory lesions on the forehead, cheeks, chin, and nose. Inflammatory nodules continued to develop across the right malar eminence and inferior to the right corner of the mouth. Postinflammatory erythema was evident, but there was no evidence of scarring (Figure 4C). By week 12, the forehead, cheeks, chin, and nose had

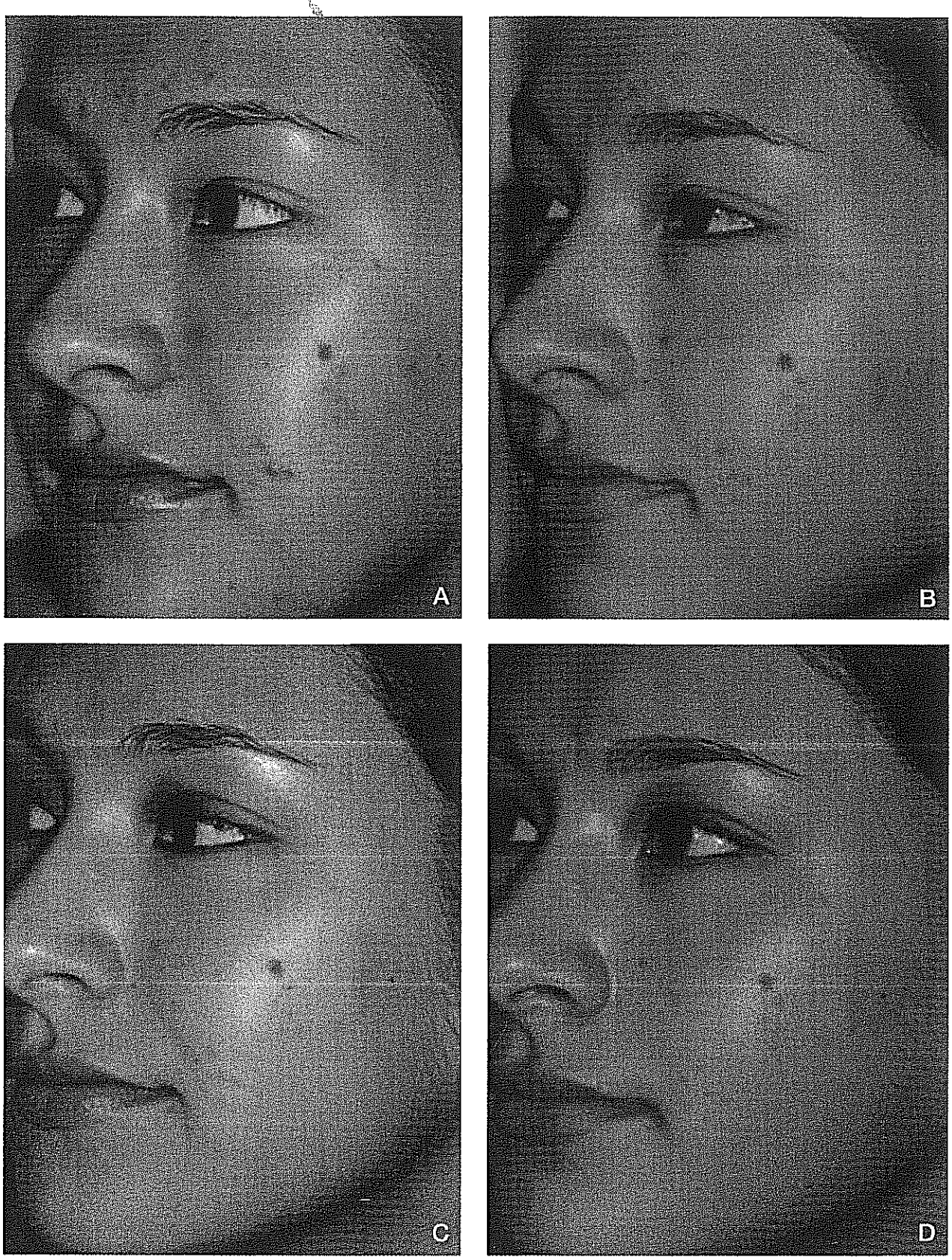


**Figure 4.** Patient with acne vulgaris at baseline (A), week 4 (B), week 8 (C), and week 12 (D) of treatment with clindamycin 1%–benzoyl peroxide 5% applied nightly with a gentle cleanser and noncomedogenic moisturizer used twice daily. At week 8, tazarotene cream 0.1% was added to the regimen.[7]

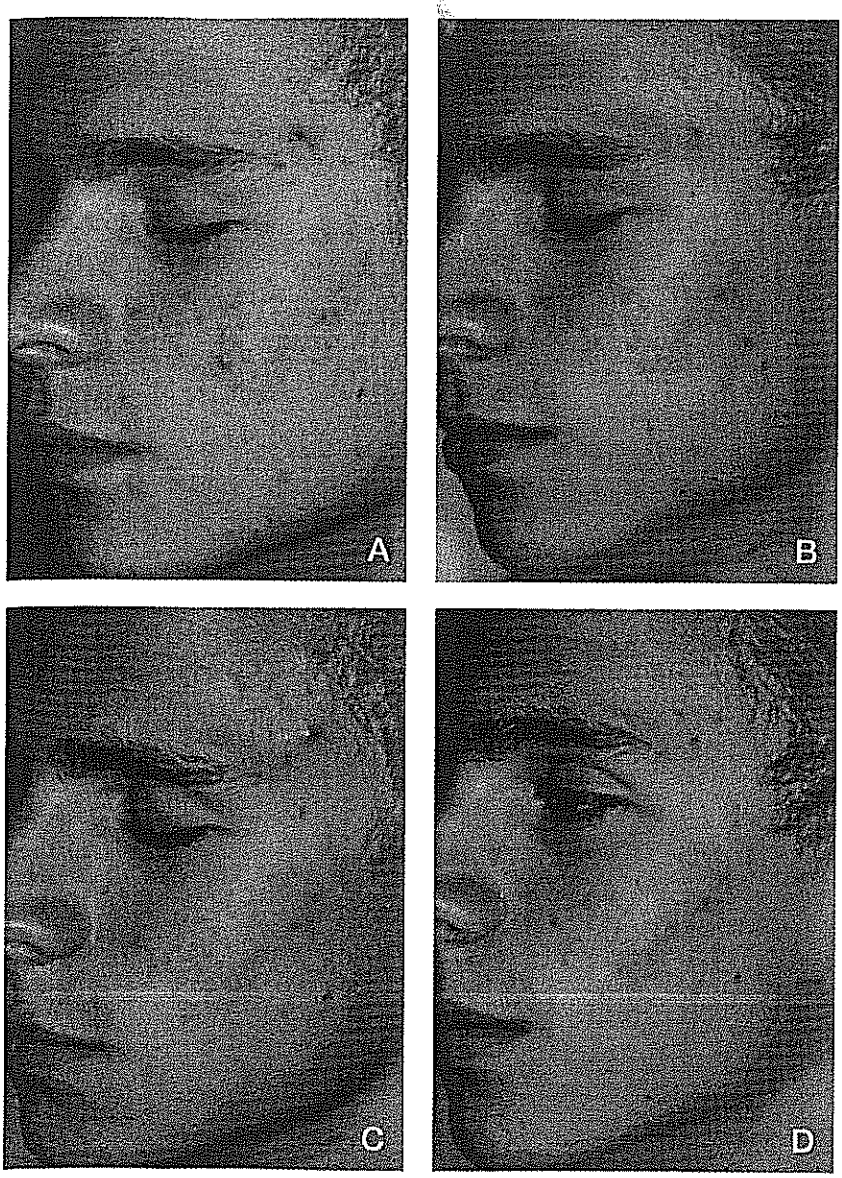


**Figure 5.** Patient with moderately severe acne at baseline (A), week 4 (B), week 8 (C), and week 12 (D) of treatment with clindamycin 1%–benzoyl peroxide 5% gel applied nightly with a gentle cleanser and noncomedogenic moisturizer.[7]

cleared, but postinflammatory erythema continued to be evident across the malar eminences and mid-third of the cheeks (Figure 4D). Treatment with the same regimen was continued.[7]

*Patient 2*—A 16-year-old white adolescent boy presented with moderately severe acne on the forehead, cheeks, and chin of 12 months' duration.[7] Prior treatment consisted of a commercial triple-product acne treatment system for 6 months before the first visit. On physical examination, the patient had open and closed comedones, papules, and pustules (Figure 5A). He was prescribed clindamycin 1%–benzoyl peroxide 5% gel to be applied nightly, and a gentle cleanser and noncomedogenic moisturizer. By week 4, a dramatic improvement was noted; the forehead was clear and there was a decrease in new lesions on the cheeks and chin (Figure 5B). At week 8, the forehead and chin were clear, though postinflammatory erythema was observed on the cheeks (Figure 5C). By 12 weeks, there was a 90% reduction in new inflammatory lesions (Figure 5D). In this case, the single-product combination produced a sufficiently dramatic improvement; additional treatments or products were unnecessary.[7]

## Conclusion

Topical clindamycin 1%–benzoyl peroxide 5% gel applied in combination with topical retinoids and sunscreens and in conjunction with oral antibiotics

appears to be a safe and efficacious treatment strategy for patients with acne. The subjects in these studies reported few treatment-related side effects, which perhaps was mitigated by the excipients in the tube gel formulation. In the trial combining clindamycin 1%–benzoyl peroxide 5% gel and topical tretinoin, the tube gel, as opposed to the jar gel, was preferred by more subjects because of better cosmetic acceptability and easier and less frequent application. Products that patients find more appealing are likely to be used more regularly, resulting in improved treatment outcomes.

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