REVIEW

# Anti-Inflammatory Properties of Clindamycin: A Review of Its Use in the Treatment of Acne Vulgaris

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**Abstract:** Topical clindamycin is a safe and effective treatment in mild to moderately-severe inflammatory acne vulgaris. Although clindamycin monotherapy often results in significant clinical improvement, clindamycin combination therapy with either benzoyl peroxide or a retinoid offers most patients a higher level of efficacy in the treatment of acne. This paper reviews the clinical efficacy and safety of clindamycin monotherapy and combination therapies, as well as an investigation into bacterial resistance against clindamycin.

**Keywords:** acne vulgaris, topical clindamycin, benzoyl peroxide, retinoids, *Propionibacterium acnes*, antibiotic-resistant acne

## Introduction

Acne vulgaris is a common inflammatory skin disorder[1] of the pilosebaceous unit, affecting approximately 70%–87% of adolescents.[2] In one large community based study in the United Kingdom, physiologic facial acne (0.25–0.75 on the Leeds acne grading scale) was seen in 54% of the adult population (ages 25 to 58), with clinical acne (1–10 on the Leeds acne grading scale) estimated at 3% in adult men and 12% in adult women.[3] Although the cause of acne is considered multifactoral, four well known factors contribute to the pathogenesis of acne: follicular epidermal hyperproliferation, a surplus of sebum production, inflammation and the concentration/action of *Propionibacterium acnes*.[4] [Conversely, a recent study did not show a correlation between *P. acnes* counts in the sebaceous material in hair follicles and the tendency to develop acne (ages 15–29 years), except in young adolescent patients (ages 10–14 years). The sample sites that reported a difference in the 10–14 age group include the nose and forehead. However, this study was conducted only in Japanese patients].[5]

Hormonal disturbances also contribute to acne flares; in women, a worsening of acne can occur during premenstrual times, and with an increase in androgens, either from an adrenal or ovarian source. The use of anabolic steroids in men can also trigger acne flaring. Additional factors in acne pathogenicity include an activation of the adaptive[6] and innate immune system by *P. acnes*, a trigger of the inflammatory cascade through proinflammatory enzymes, cytokines and chemokines,[7] along with neutrophil inflammatory factors capable of bursting the wall of the follicle.[8]

Interestingly, recent studies suggest that keratinocytes and sebocytes also play a role in the formation of acne. It is believed that sebocytes induce the innate immune system through lipid metabolism,[9] the production of antimicrobial peptides, and proinflammatory cytokines/chemokines.[10] More specifically, on a molecular level, pattern recognition receptors (ex: Toll-like receptors) recognize pathogen-associated molecular patterns (ex: lipopolysaccharide of gram-negative bacteria) as part of the innate immune system, and are of importance in the pathogenesis of acne, as both keratinocytes and sebocytes are believed to express these receptors. Therefore, it is thought that

*P. acnes* plays a vital role in triggering the immune system through Toll-like receptors, in addition to CD1d molecules, which activate natural killer T cells through the presentation of abnormal lipid antigens.[11]

Various grading systems, such as the Leeds technique, the acne lesion-counting technique, the American Academy of Dermatology classification and the Global Acne Grading System, among others, have been established to classify acne vulgaris. However each grading system contains possible pitfalls. For example, the Global Acne Grading System divides the face/chest/upper back into six regions, with each region receiving a calculated grade (determined through lesion types) and a pre-determined factor (based on the region's surface area, and the concentration and distribution of pilosebaceous units). The sum of the regions corresponds to a global score relating to the severity of acne; however if one region has a much higher proportion of lesions than other regions, the total grade will be lower than what is found clinically.[12] Therefore, clinicians should note the variability that each system is subjected to that at times can result in questionable validity.

Nonetheless, most acne grading systems divide acne lesions into mild, moderate and severe, along with the presence or tendency for scarring. Several types of acne lesions can be present, namely, comedones, papules, pustules, and nodules.[13] Therapies are chosen based on acne severity as well as the types of lesions present.

Antimicrobials have been widely used in the treatment of acne for well over 30 years.[14] Since that time, numerous studies have investigated the efficacy, safety, and side effects of such treatments. Over time new formulations and combinations of antimicrobial treatments have been introduced. Topical clindamycin is a popular antimicrobial used to treat mild to moderately severe acne with a predominance of inflammatory lesions. This review focuses on the mechanism of action, efficacy, safety, tolerability and clinical applications of topical clindamycin alone and in combination with benzoyl peroxide and topical retinoids.

## Pharmacology
### Mechanism of action and antimicrobial susceptibilities

Clindamycin is a semi synthetic drug, derived from the lincosamide antibiotics.[15] Clindamycin exerts its antimicrobial effects through the binding of the 50S

bacterial ribosomal subunit, thereby inhibiting bacterial protein synthesis.[15–17] In a review of topical antibiotics, clindamycin was shown to have three mechanisms of action: (1) A reduction in percent surface free fatty acids, (2) Anti-inflammatory properties, and (3) A decrease in the number of propionibacteria.[18]

Of these mechanisms of action, particular interest is found in further investigating the role of clindamycin in inhibiting the inflammation that accompanies acne vulgaris. Specific anti-inflammatory properties of clindamycin include an inhibition of the growth, protein synthesis, lipase production, follicular free fatty acid production and leukocyte chemotactic molecules in *P. acnes*. Additionally clindamycin results in an inhibition of the respiratory burst, iNOS enzymes and multiple proinflammatory cytokines (IL-1β, IL-6, IFN-γ, and TNF-α).[7]

The role of antibiotics on human leukocyte chemotaxis was investigated using an in vitro assay. Results showed that clindamycin HCL (Upjohn Company, Kalamazoo, Michigan) did inhibit the migration of white blood cells at concentrations of 0.2 µg/ml, 2 µg/ml, 20 µg/ml and 200 µg/ml, resulting in a statistically significant difference ($P \leq 0.0005$) at all concentrations. Additionally, some effect was seen with the lower concentrations of clindamycin (0.2, 2, and 20 µg/ml) on random migration, ($P = 0.01$, 0.01, $<0.1$ respectively).[19] Thus clindamycin does play an important role in the inflammatory response.

Organisms susceptible to clindamycin include anaerobes (peptococci, peptostreptococci, propionibacteria, *C. perfringens*, and fusobacteria), some protozoa such as *Toxoplasma gondii,* and many Gram-positive cocci (most *Streptococcus* species, MRSA, and *Staphylococcus epidermidis*).[17] Most Gram-negative organisms are not susceptible to clindamycin.[15] Clindamycin is a popular drug in dermatology due to its actions against *Propionibacterium acnes* and many skin infections caused by *Streptococcus* and *Staphylococcus* species.

## Pharmacokinetics
### Absorption
Oral clindamycin is almost fully absorbed, regardless of the presence of food.[16] Since topical clindamycin is frequently prescribed to treat acne vulgaris, we have focused our attention on presenting studies examining transdermal absorption rates, as measured through plasma and urine analysis.

Barza et al[20] measured transdermal absorption levels in African American and Caucasian acne patients after using 2 ml topical 1% clindamycin hydrochloride twice daily for four weeks. Thirteen subjects' serum and urine was analyzed on the third and twenty-seventh day of treatment. Clindamycin was not detected in any of the patients' serum ($<0.4$ µg/ml). However clindamycin was detected in the urine of ten out of the thirteen patients, with individual levels being fairly constant when measured on days three and twenty-seven ($P < 0.0001$). Urine levels of clindamycin varied considerably between patients ranging from $<10$ to 500 µg/day. There was no correlation between skin color and the amount of clindamycin excreted in the urine. This study concludes that small amounts, in the range of 4%–5%, of topical 1% clindamycin hydrochloride are absorbed systemically, with some patients absorbing more.

A second study by van Hoogdalem et al[21] also measured transdermal absorption in three topical clindamycin products: 1% clindamycin phosphate/0.025% tretinoin gel, 1% clindamycin hydrochloride/0.025% tretinoin gel, and a 1% clindamycin phosphate lotion in twelve males. Subjects used all three preparations for five days each, with 2.5 week wash-out periods in between treatments. Blood and urine samples were taken on the fifth day of treatment. Plasma levels did not exceed 5 ng/ml (the limit of quantification), in eleven patients taking the clindamycin phosphate preparations. One patient did have an average plasma level of 8 ng/ml from the clindamycin hydrochloride/tretinoin preparation only. Urinary excretion showed higher clindamycin levels with clindamycin hydrochloride (23 µg/12 h) in comparison with the other two clindamycin phosphate preparations, (11 µg/12 h for clindamycin phosphate/tretinoin gel and 10 µg/12 h for clindamycin lotion). A statistically significant difference ($P < 0.05$) was shown between the clindamycin phosphate lotion and clindamycin hydrochloride/tretinoin gel in urinary clindamycin excretion levels. Further studies with this group of researchers measured both tretinoin and clindamycin levels from daily topical clindamycin phosphate/tretinoin gel or tretinoin use after four and twelve weeks in forty moderate to severe acne patients. Plasma tretinoin and clindamycin levels were non-quantifiable in most

samples after twelve weeks. Exceptions include two patients with a tretinoin plasma level ranging from 3–5 ng/ml and five clindamycin plasma samples with levels ranging from 3.1–10.9 ng/ml.

A third study by Chassard et al[22] examined systemic exposure after topical administration of zinc acetate/1% clindamycin phosphate gel and 1% clindamycin phosphate lotion. Twenty-four subjects with mild to moderate acne applied each medication twice daily for five days, with a two week wash out period in between treatments. Plasma levels revealed that systemic absorption of clindamycin was low for both treatments, but was about 30%–50% less with zinc/clindamycin gel than with clindamycin lotion. This suggests that zinc may offer some protection against systemic exposure to clindamycin.

Eller et al[23] studied absorption kinetics of clindamycin when given topically and intravenously in twelve Caucasian males without acne. Each patient underwent three different treatments consisting of an IV infusion of 300 mg of clindamycin phosphate over 10 minutes, 1 ml of topical clindamycin phosphate solution every 12 hours for 4 days, and 1 ml of topical clindamycin HCl every 12 hours for 4 days, with appropriate washout periods in between treatments. Roughly 13% of the IV dose of clindamycin was detected in the urine, with a calculated half-life of 0.7 hours and an elimination time of 2.9 hours. After topical administration, clindamycin was found in the urine of all patients during both topical treatments. Urine clindamycin levels were significantly higher when taking the HCl form in comparison to the phosphate form ($P < 0.05$). Peak serum concentrations for topical clindamycin phosphate were <0.5 ng/ml to 6 ng/ml and 4–20 ng/ml for topical clindamycin HCL. This study suggests that systemic exposure is minimal when using topical clindamycin, but may be dependent on the vehicle formulation.

### Metabolism, distribution and excretion

Clindamycin is metabolized in the liver and excreted in the urine, bile[17] and feces.[16] Distribution includes most tissues except the cerebrospinal fluid; however clindamycin can accumulate in a high enough concentration in the cerebrospinal fluid to treat cerebral toxoplasmosis.[16] Collection occurs in polymorphonuclear leukocytes,[16,17] alveolar macrophages and abscesses.[16] Clindamycin does cross the placenta.[16]

Half-life is approximately three hours and most of the drug is attached to plasma proteins.[16]

### Dosage

Clindamycin is available orally and topically as a solution, gel, or lotion as well as a vaginal cream.[16] Oral dosage in adults is 150–300 mg every 6 hours and in severe infections 300–600 mg every 6 hours. Care must be taken in patients with liver failure, as the dose may need to be adjusted.[16] Topical clindamycin is currently available as clindamycin phosphate 1% in a gel, foam, solution, or lotion, and 1%–1.2% when combined with benzoyl peroxide or topical retinoids.

## Pharmacodynamics

Clindamycin is bacteriostatic with a normal dose and possibly bactericidal with increased concentrations.[15]

## Side effects

Topical clindamycin is a relatively safe and highly tolerable drug in the treatment of acne vulgaris. Common side effects reported include dryness, peeling, burning, erythema and pruritus, but are most often seen in combination therapy with benzoyl peroxide or topical retinoids (clinical studies-patient preference section). Although rare, serious adverse events have been reported, including tinnitus, diarrhea and two reports of pseudomembranous colitis. These cases are reported in further detail below.

Tinnitus has been documented in a 14 year old Caucasian male acne patient while applying clindamycin pledgets for a few weeks. The boy reported mild, periodic ringing in his right ear, which later turned into hearing loss. He was then prescribed 1% clindamycin/5% benzoyl peroxide for his acne vulgaris, and experienced more severe buzzing in his right ear 2–3 months after the start of treatment. When he stopped clindamycin/benzoyl peroxide, the tinnitus had improved. His tinnitus continued a third time after he began clindamycin/benzoyl peroxide and stopped after discontinuing the medication.[24]

A case report[25] in 1987 revealed a 26 year old male given 1% topical clindamycin solution twice daily for acne. He soon developed frequent, loose, watery stools after several days of therapy. Upon discontinuation of clindamycin, the diarrhea ceased. The patient decided to try the medication a second time, which

induced the diarrhea a second time, with cessation when treatment was stopped.

Two reports of patients treated with topical clindamycin were later diagnosed with pseudomembranous colitis. One reports of a 24 year old prescribed topical 1% clindamycin hydrochloride to be applied once daily in the morning with 5% benzoyl peroxide to be applied in the evening for facial acne. However the patient used both medications twice daily. After five days of this therapy the patient developed progressing abdominal cramping and diarrhea, and was later found to have 1:200 titer of *C. difficle* toxin. She underwent a sigmoidoscopy and colonic biopsy and was diagnosed with pseudomembranous colitis, which was treated successfully with oral vancomycin. The patient was not taking any medications before starting the acne regimen and had no prior medical history, travel history or GI complaints.[26]

A second case report describes a 42 year old woman treated with topical clindamycin phosphate for facial acne off and on for a period of 6 months. She went on to develop abdominal pain, diarrhea, and fever. A positive stool assay for *C. difficle* toxin was found and symptoms were alleviated after metronidazole therapy. She then went back to using clindamycin phosphate twice daily. After one week, she again experienced abdominal pain, diarrhea and fever, along with a positive *C. difficle* toxin assay, which was treated successfully with oral vancomycin. The patient no longer used topical clindamycin therapy and reported no further complaints. Prior medical and medication history was negative, except for Down's syndrome.[27]

Although pseudomembranous colitis is a rare and infrequent potential complication, studies have been conducted to analyze the impact topical clindamycin may have on intestinal flora. Siegle et al[28] conducted a randomized, double-blind study examining the effect of topical 1% clindamycin phosphate applied twice daily versus placebo on intestinal microflora in acne patients for eight weeks. Stool cultures taken during treatment showed that four of the nineteen patients using the clindamycin solution and none of the ten vehicle patients had *C. difficile* identified; this difference was not significant ($P = 0.16$). Clindamycin was not found in the urine or stool of any individual, and none of the patients in the clindamycin group had diarrhea. *Bacteroides fragilis*, a bacterium that is susceptible to clindamycin, was not significantly different between the two groups as measured through stool counts. This study suggests that topical clindamycin phosphate does not significantly alter bowel flora.

## Safety
Care should be taken if prescribing topical clindamycin to pregnant or nursing women, as this drug is classified as FDA category B. Topical clindamycin is also not recommended for patients with regional enteritis, ulcerative colitis or antibacterial-associated colitis.[29]

## Drug interactions
Clindamycin may increase the effect of neuromuscular blocking agents, if taken together.[16] Clindamycin should also not be given with other antibiotics, (ie, erythromycin, chloramphenicol) that bind to a similar location on the bacterial ribosome.[16]

## Antibiotic resistance
Resistance to clindamycin can come about in different ways, with the most common being the bacterium changing the binding site.[15,17] Clindamycin resistant propionibacteria is on the rise in acne patients. In ten year surveillance study beginning in 1991 by Coates et al,[30] antibiotic resistant propionibacteria was measured on the skin in 4,274 acne patients. Resistance to erythromycin, clindamycin and tetracycline was documented. As suspected, antibiotic resistance to at least one of the commonly used antibiotics for acne rose from 34.5% in 1991 to 55.5% in 2000. Erythromycin resistance was the most widespread with most of the propionibacteria also possessing a cross resistance to clindamycin. However, clindamycin resistant strains were always less than erythromycin resistant strains.

Recent studies have investigated the ability of *P. acnes* to form biofilms in the pilosebaceous unit, consequently creating a shielded microenvironment and local inflammatory reaction, often leading to prolonged infections and an increase in resistance to antimicrobial treatments. Thus, the aspect of *P. acnes* and biofilm formation should be ascertained in the treatment of acne vulgaris. *P. acnes* nestled in biofilms can exhibit resistance to antibiotics, even in elevated concentrations; therefore standard bacterial cultures, which do not take into account biofilm formation, are often not reliable in predicting antibiotic resistance.

Therefore, therapies with the ability to change the micro environment of the pilosebacous unit, such as products effecting cell proliferation and differentiation, may prove beneficial in penetrating biofilms, in addition to topical and oral antibiotics.[31]

An in-vitro study examined the antimicrobial susceptibilities of *Propionibacterium acnes* isolates which had colonized and formed biofilms on four different orthopedic biomaterials used in hip replacements. Interestingly, *Propionibacterium acnes* had previously been categorized as a skin contaminant, but as a result of this study, is now viewed as a bacterium with the potential to cause a low-grade chronic infection in biomaterials. Results showed that half of the *P. acnes* strains are sensitive to gentamicin with the other half demonstrating a two or four fold increase in resistance. In addition, all strains showed resistance to cefamandole, ciprofloxacin and vancomycin.[32] This study further illustrates the hardiness of *P. acnes*, and potential barriers that must be overcome to achieve successful treatment.

## Clinical Studies

Search sources: PubMed, Medline, clinical evidence.

Search strategy: Keywords used in this search include "topical clindamycin and acne vulgaris", "clindamycin monotherapy and acne vulgaris", "clindamycin and benzoyl peroxide", "topical clindamycin antimicrobial resistance in acne patients", and "topical clindamycin and patient preference". Randomized controlled trials (RCTs) in the clinical studies efficacy section were selected based on minimum criteria of investigator or double blinded, randomized, with at least a 10-week treatment duration, as well as documentation of acne severity or lesion counts and the reduction of total, inflammatory, and/or non-inflammatory lesions.

RCTs in the clinical studies *Propionibacterium* species section were selected based on investigator or double blinded, randomized, as well as documentation of *Propionibacterium* counts. Two studies in this section (Leyden et al, 2001 and Leyden 2002) were open-label studies in healthy volunteers.

Many of the RCTs in the patient preference section were initially listed in the clinical studies efficacy section and thus follow the selection criteria as listed above; studies limited to this section only

did not have a treatment duration or documentation of lesion counts prerequisite, but must have detailed documentation of side effects and tolerability. In addition, two studies were open-label (Weiss et al[48] and Kircik et al[50]) and one study (Tucker et al[47]) did not include documentation of a blinded, randomized study.

## Efficacy

Topical clindamycin is a common medication prescribed to treat inflammatory lesions in mild to moderately severe acne vulgaris. It can be used singly, or in combination with other acne products including benzoyl peroxide and topical retinoids. Table 1 shows studies revealing the efficacy of various formulations of topical clindamycin as measured through the percent reduction of inflammatory, non-inflammatory and total lesion counts.

### Clindamycin monotherapy formulations versus placebo

Several studies examined the efficacy of different formulations of clindamycin compared to each other and placebo. One study showed that clindamycin 1% gel and 1% solution demonstrate a similar effectiveness, with superiority over placebo.[33] A second study compared topical 1% clindamycin/zinc gel applied once or twice daily with 1% clindamycin lotion applied twice daily in mild to moderate acne patients. Both formulations demonstrated a similar effectiveness in the reduction of total inflammatory lesions at both 12 weeks ($P = 0.203$) and 16 weeks ($P = 0.626$), along with a parallel reduction in non-inflammatory ($P = 0.769$) and total lesion counts ($P = 0.707$). Neither formulation demonstrated inferiority to the other in regards to efficacy. Clindamycin/zinc gel showed a comparable effectiveness whether applied once or twice daily.[34] Shalita et al[35] examined a gel and a foam formulation of topical 1% clindamycin along with their respective vehicles in 1,026 mild to moderate acne patients for 12 weeks. Clindamycin foam achieved statistical significance in the reduction of inflammatory ($P = 0.0478$), non-inflammatory ($P = 0.0037$) and total acne lesions counts ($P = 0.0014$) in comparison to the clindamycin gel. Clindamycin foam was also superior to the vehicle foam in the reduction of inflammatory, non-inflammatory and total lesion counts ($P < 0.05$).

### Clindamycin/benzoyl peroxide versus placebo and monotherapy

Four studies prove a statistically significant superiority of clindamycin/benzoyl peroxide in the reduction of inflammatory, non-inflammatory and total lesions counts in comparison with clindamycin alone, benzoyl peroxide alone, and placebo therapy.[36–38] The fourth study by Leyden[39] also investigated 1% clindamycin/5% benzoyl peroxide in comparison to 5% benzoyl peroxide, 1% clindamycin and placebo alone in 480 patients with moderate to moderately severe acne for 10 weeks. Results demonstrated that combination therapy showed the highest effectiveness in reducing inflammatory lesions in comparison to clindamycin alone and placebo at week 2 ($P \leq 0.0003$), and with benzoyl peroxide alone at week 6 ($P \leq 0.0022$) continuing through week 10. Clindamycin/benzoyl peroxide also demonstrated the highest effectiveness in the reduction of total lesions compared with clindamycin and placebo at week 2 ($P < 0.0001$) and with benzoyl peroxide alone at week 6 ($P \leq 0.0184$) and continued through week 10.

### Clindamycin/topical retinoid versus placebo and monotherapy

Two groups of 249 total acne patients applied 1% clindamycin phosphate lotion twice daily along with 0.1% adapalene gel once every evening, or a gel vehicle once every evening with 1% clindamycin phosphate lotion twice daily for twelve weeks. All lesion counts showed a statistically significant difference favoring the clindmycin and adapalene group over the clindamycin and vehicle group.[40] Similar results were seen with clindamycin/tretinoin.[41] When comparing clindamycin/benzoyl peroxide to adapalene alone, a higher reduction along with a statistically significant difference was seen in all lesion counts using the clindamycin/benzoyl peroxide in comparison to adapalene alone.[42]

Del Rosso[43] compared the efficacy of three different acne formulations in 109 patients: (1) Clindamycin 1%/benzoyl peroxide 5% gel every morning for 4 weeks, after which adapalene 0.1% gel was applied in the evening for the next eight weeks, (2) Adapalene 0.1% gel applied in the evening for 12 weeks, (3) Clindamycin 1%/benzoyl peroxide 5% gel in the morning and adapalene 0.1% gel in the evening for 12 weeks. After 12 weeks, the combination treatment groups had a higher percent reduction in inflammatory, noninflammatory and total lesion counts in comparison to adapalene alone, further illustrating the efficacy of combination therapy.

### Clindamycin versus topical erythromycin.

Langer et al[44] compared topical 1% clindamycin phosphate/5% benzoyl peroxide in 73 patients to erythromycin/zinc in 75 patients with mild to moderate acne for twelve weeks. Clindamycin/benzoyl peroxide proved more effective in the median percentage improvements in non-inflammatory, inflammatory and total lesion counts in comparison to erythromycin/zinc. Clindamycin/benzoyl peroxide also showed a statistically significant difference at week 2 in total lesion count ($P = 0.017$) and inflammatory lesion count ($P = 0.029$) improvement; however significance was not achieved between the two therapies at any other time point.

A recent systematic review examined the effectiveness of topical erythromycin and clindamycin in acne clearance dating back to the 1970s. Results showed no evidence of a decrease in efficacy of clindamycin. Erythromycin however did show a decrease in clinical effectiveness in the reduction of inflammatory lesions; reports documented a 40%–60% reduction in inflammatory lesions up until the 1990s to roughly a 20% reduction in the late 1990s to early 2000s. A significant difference was reported in erythromycin's clinical effectiveness when used for a twelve week duration in both inflammatory ($P = 0.001$) and noninflammatory lesion counts ($P = 0.001$) during this time period.[45]

## Topical clindamycin and *propionibacterium* spp.: reduction and resistance

While we recognize the debate over bacterial resistance and its influence over the anti-acne effectiveness of antibiotics, we address the role of topical clindamycin resistance in acne treatment in a review of these five papers. Three randomized, controlled, and at least investigator blind studies are listed in Table 2[34,36,42] along with two open-label, comparative studies.[47,48]

**Table 1.** Topical clindamycin versus placebo, benzoyl peroxide, retinoids and combination products in the treatment of acne vulgaris.

| Reference | No. of patients | Acne severity | Treatment | Reduction of inflammatory lesions, % |
|---|---|---|---|---|
| **Clindamycin vs. placebo** | | | | |
| Alirezai et al,[33] | 592 | Moderate¥ | Clin[a]-1% gel (1) vs. | 62 |
| | | | clin-1% solution (2) vs. | 64* |
| | | | vehicle gel (3) for 12 weeks | 51 |
| **Clindamycin vs. benzoyl peroxide vs. combination products** | | | | |
| Cunliffe et al,[36] | 79 | Mild-moderate | CDP[b] 1%/BPO[c] gel 5% vs. | 48* |
| | | | clin 1% gel for 16 weeks | 30* |
| Lookingbill et al,[37] | 334 | Mild-moderate¥ | CDP 1%/BPO gel 5% (1) vs. | 61 |
| | | | CDP 1% gel (2) vs. | 35 |
| | | | BPO 5% gel (3) vs. | 39 |
| | | | vehicle gel (4) for 11 weeks | 5 |
| Webster et al,[38] | 2,813 | Moderate | CDP 1.2%/BPO2.5% gel (1) vs. | 56 |
| | | | CDP 1.2% (2) vs. | 68 |
| | | | BPO 2.5% (3) vs. | 58 |
| | | | placebo (4) for 12 weeks | 36 |
| | | Severe | CDP 1.2%/BPO2.5% gel (1) vs. | 49 |
| | | | CDP 1.2% (2) vs. | n/a |
| | | | BPO 2.5% (3) vs. | n/a |
| | | | placebo (4) for 12 weeks | 24 |
| **Clindamycin vs. retinoid combinations** | | | | |
| Wolf et al,[40] | 249 | Mild-moderate | CDP 1% lotion/adaplane gel 0.1% vs. | 55 |
| | | | CDP 1% lotion/vehicle for 12 weeks | 44 |
| Zouboulis et al,[41] | 209 | Moderate-severe | clin 1%/tretinoin 0.025% gel | 44.5[g] |
| | | | vs. clin 1% lotion for 12 weeks | 31 |
| Langer et al,[42] | 130 | Mild-moderate | CDP 1%/BPO 5% gel vs. | 82* |
| | | | adapalene 0.1% gel for 12 weeks | 56* |
| Del Rosso,[43] | 109 | n/a | CDP/BPO + AP8[d] (1) vs. | 60 |
| | | | AP12[e] (2) vs. | 58 |
| | | | CDP/BPO + AP12 (3) | 71 |
| Zouboulis et al,[46] | 382 | Moderate-severe¥ | clin 1%/BPO 5% gel HE[f] vs. | 77 |
| | | | adapalene 0.1%/BPO 2.5% gel for 12 weeks | 72 |

Clindamycin/zinc gel applied once or twice a day and clindamycin lotion applied twice a day were compared to assess the reduction and resistance rates of *Propionibacterium* spp. with each therapy. All treatments demonstrated a similar effectiveness in the reduction of *Propionibacterium* spp. skin surface counts. Although resistant counts to topical clindamycin did increase during treatment, no significant difference was found between the three therapies, and resistance strains were less than 5% in all groups.[34]

A second study[47] examining *P. acnes* reduction rates with several formulations of clindamycin showed the most favorable results with clindamycin/benzoyl

| P value | Reduction of non-inflammatory lesions, % | P value | Total reduction of lesions, % | P value |
|---|---|---|---|---|
| 1 vs. 3 = 0.006; 1 vs. 2 = NS[+] | n/a˜ | n/a | 52*<br>54<br>50 | 1 vs. 3 = 0.009 |
| 0.035[†] | 44*<br>21* | 0.046[†] | 53<br>27.5 | 0.013[†] |
| (1,2,3) vs. (4) ≤0.002 @ 2–11 weeks<br>(1) vs. (3)<0.02 @ 2, 8, 11 weeks<br>(1) vs. (2)<0.02 @ 2, 5, 8, 11 weeks<br>(2) vs. (3) = NS[+] | 36*<br>8*<br>28*<br>−11* | (1) vs. (4) ≤0.004 @ 2–11 weeks<br>(3) vs. (4) ≤0.005@ 5–11 weeks<br>(2) vs. (4) = 0.04@ 11 weeks<br>(1, 3) vs. (2) ≤0.01 (throughout study)<br>(1) vs. (3) = NS[+] | n/a | n/a |
| (1) vs. (4) <0.001<br>(1) vs. (2, 3) <0.001 | 50<br>41<br>44<br>25 | (1) vs. (2) = 0.001<br>(1) vs. (3) = 0.001<br>(1) vs. (4)<0.001 | 54<br>45<br>47<br>30 | (1) vs. (2) <0.001<br>(1) vs. (3) <0.001<br>1) vs. (4)<0.001 |
| (1) vs. (4) <0.001 | 45<br>n/a<br>n/a<br>27 | (1) vs. (4) <0.001 | 44<br>n/a<br>n/a<br>19 | (1) vs. (4) <0.001 |
| 0.004[†] | 42.5<br>16 | <0.001[†] | 47<br>25.5 | <0.001[†] |
| 0.018[†] | 69<br>61 | 0.05[†] | n/a | n/a |
| ≤0.001[†] | 62*<br>48* | ≤0.05[†] | 70*<br>52* | <0.005[†] |
| NS[+] | 60<br>61<br>71 | (3) vs. (2) <0.05 | 61<br>52<br>71 | (3) vs. (2) <0.05 |
| 0.076[†] | 62<br>61.5 | n/a | 69<br>67 | 0.42[†] |

**Notes:** [¥]severity estimated from lesion counts; *data estimated from graph; ˜n/a, data not available; [a]clindamycin, [b]clindamycin phosphate, [c]benzoyl peroxide, [†]between group comparisons, [+]NS, not significant, [d]AP8, adapalene 0.1% gel for 8 weeks; [e]AP12, adapalene 0.1% gel for 12 weeks; [f]HE, hydrating excipients; [g]absolute percent reduction.

peroxide gel in comparison to clindamycin gel, solution, and lotion. When reported as mean percent reductions after 2 weeks, clindamycin/benzoyl peroxide showed a 99.9% reduction, with clindamycin gel, lotion, and solution showing an 89%, 88%, 94% reduction respectively. Thus, the greatest reduction in *P. acnes* counts was achieved with combination therapy.

Cunliffe 2002[36] examined clindamycin/benzoyl peroxide and clindamycin alone in the reduction and resistance rates of *P. acnes*. Reported percent reductions in *P. acnes* counts with clindamycin/benzoyl peroxide reached 99% after four weeks and continued throughout the course of treatment. Clindamycin alone achieved a reduction of 85.3%, 96.5%, 92.1% and 87.9% at

**Table 2.** Topical clindamycin formulations and the reduction and resistance rates of *Propionibacterium spp*.

| Reference | No. of patients | Acne severity | Treatment | *Propionibacterium* counts ($\log_{10}$ cfu*/cm²)[a] | Resistant *propionibacterium* counts ($\log_{10}$ cfu/cm²) |
|---|---|---|---|---|---|
| Cunliffe et al,[34] | 67 | Mild-moderate | Clin[†] 1% zinc gel qd vs. clin 1% zinc gel bid vs. clin 1% lotion bid | Week 16<br>0.147<br>1.260<br>0.755 | 0.331<br>1.088<br>0.527 |
| Leyden et al,[47] | 80 | n/a[b] | Clin 1%/BPO[¥] 5% gel vs. clin 1% gel vs. clin 1% solution vs. clin 1% lotion | (Baseline, week 1, week 2)<br>6.32, 2.71, 3.08<br>6.05, 0.16, 1.03<br>6.15, 0.47, 1.34<br>6.24, 0.36, 0.91 | n/a |
| Langer et al,[42] | 40 | Mild-moderate | CDP[+]/BPO vs. adapalene 0.1% gel | (Baseline, week 12/discontinuation)<br>4.370, 3.13<br>4.412, 4.914 | 1.634, 0.832 (clin)<br>1.999, 1.093 (ery)[€]<br>1.441, 1.528 (clin)<br>2.162, 2.288 (ery) |
| Cunliffe et al,[36] | 79 | Mild-moderate | CDP 1%/BPO gel 5% vs. clin 1% gel | Week 16<br>−2.1<br>−0.9<br>$P = 0.002$ | −0.2<br>1.2<br>$P = 0.018$ |
| Leyden,[48] | 59 | n/a[b] | CDP1%/BPO gel 5% vs. CDP 1% solution vs. vehicle gel | (Baseline, week 2)<br>6.2, 3<br>6.3, 0.64<br>6.5, −0.1[±] | n/a |

**Notes:** *cfu, colony forming units; [a]Clinical importance is typically achieved with a mean log change of at least one;[34] [†]clin, clindamycin; [¥]BPO, benzoyl peroxide; [+]CDP, clindamycin phosphate; [±]data estimated from graph; [€]erythromycin; [b]patients had ≥10,000 colonies/cm² of *P. acnes* on forehead.

weeks 4, 8, 12, and 16 respectively. After 16 weeks, combination therapy demonstrated a statistically significant difference in a higher reduction count ($P = 0.002$) and lower clindamycin resistance count ($P = 0.018$) of *P. acnes* in comparison to clindamycin monotherapy.

Similar results in the reduction of *P. acnes* were shown in another study comparing clindamycin/benzoyl peroxide gel, clindamycin phosphate solution or vehicle gel to the forehead twice daily for two weeks in 59 patients. Patients did not have clinical acne, but demonstrated high concentrations of *P. acnes* under a Wood's lamp. Both treatments did have a statistically significant reduction in *P. acnes* counts compared to baseline values; combination therapy (clindamycin/benzoyl peroxide) showed significance after 24 and 72 hours and week 1 and 2 ($P < 0.001$), along with clindamycin phosphate after week 2 ($P < 0.05$). When reported as percent inhibition of *P. acnes*, clindamycin/benzoyl peroxide had a 91%, 99%, and 99.9% after 24 hours, week 1 and week 2 respectively, with monotherapy (clindamycin phosphate) demonstrating a 31%, 63%

77% inhibition after 24 hours, 72 hours and week 2 respectively.[48]

When clindamycin/benzoyl peroxide was compared to adapalene (topical retinoid), clindamycin/benzoyl peroxide demonstrated a higher reduction of propionibacteria and a lower count of resistant bacteria after 12 weeks/discontinuation of study, while adapalene showed an increase in propionibacteria count as well as more resistant organisms.[42] Adapalene (topical retinoids) has a different mechanism of action compared to clindamycin/benzoyl peroxide; therefore use of both agents in acne may be warranted.

On a broader scale, studies have shown that the efficacy of antibiotics may also be related to their anti-inflammatory properties. For example, at sub-minimum inhibitory concentrations, tetracyclines and erythromycin were able to reduce the ability of *P. acnes* to produce neutrophil chemotactic factors, thereby decreasing the potential for inflammatory reactions.[49] Thus, antibiotics in acne may still produce a desired therapeutic effect due to anti-inflammatory properties, despite possible antibiotic resistance.

# Patient preference-irritancy, tolerability, side-effects

Due to the vast number of acne products available, patient compliance is best with treatments that are the most tolerable with minimal side effects. Below are several studies that have evaluated patient preference with different formulations of clindamycin and other acne therapies.

## Clindamycin monotherapy

In comparing 1% clindamycin foam, 1% clindamycin gel, vehicle foam and vehicle gel, all groups experienced treatment adverse events (8%, 3%, 13%, and 5% respectively), with the most frequent side effect being burning at the application site (6%, 1%, 7%, 2% respectively). Other common complaints include dryness, application site reaction and pruritus. However the authors described these adverse events as "mild or moderate and transient in nature".[35]

A study out of the U.K. examined patient preferences of four topical antibiotic treatment regimens for acne vulgaris using a conjoint analysis and patient questionnaires. One week application of each medication (erythromycin/zinc solution BID, clindamycin phosphate lotion BID, benzoyl peroxide/erythromycin gel BID and clindamycin phosphate gel once daily) was enforced in 64 mild to moderate acne patients. Questionnaire results showed that clindamycin phosphate gel was the medication liked by the most patients and was the easiest to apply. Both clindamycin phosphate gel and lotion were rated the best for making the skin feel pleasant. The number of adverse events (including dry skin, aggravation of acne, pain and skin tightness) was lowest with clindamycin phosphate gel and lotion in comparison with the other two medications. These side effects were described as "mild and transient". Patient ranking of overall satisfaction was highest with clindamycin phosphate gel, followed by clindamycin phosphate lotion, benzoyl peroxide/erythromycin gel and erythromycin/zinc solution. The conjoint analysis found that the patients preferred a gel medication applied with fingers once daily, with a product lifespan of 18 months when opened.[50]

## Clindamycin/benzoyl peroxide versus monotherapies and placebo

In a study comparing the safety of clindamycin/benzoyl peroxide gel, clindamycin gel, benzoyl peroxide gel and a vehicle gel, reported adverse events were fairly analogous in all acne regimens, ranging from 20.0% to 29.2%. Adverse events were highest in the benzoyl peroxide group, followed by combination therapy (clindamycin/benzoyl peroxide), vehicle and clindamycin. The most common side effect was dry skin, and was highest (9.2%) in the benzoyl peroxide and combination therapy and lowest (5%) in the both clindamycin and vehicle groups.[39]

A second study investigated the same treatment groups as listed above and showed similar results. Overall tolerance in all treatment groups was excellent, ranging between 93.5% to 95.5%, with the lowest percentage seen with benzoyl peroxide, followed by clindamycin/benzoyl peroxide, clindamycin, and vehicle. Clindamycin/benzoyl peroxide had the highest percentage of patients experiencing peeling, dryness, burning, and pruritus, while clindamycin had the lowest percentage of patients reporting erythema, peeling, dryness, burning or pruritis. Local irritation did not reach statistical significance between the three treatment groups in comparison to vehicle. Peeling reached significance ($P < 0.02$) in the clindamycin/benzoyl peroxide and benzoyl peroxide monotherapy groups versus clindamycin.[37]

A third study comparing clindamycin/benzoyl peroxide to clindamycin alone also showed a higher incidence of mild to moderate adverse events in the combination group in comparison to monotherapy. Dry skin, application site reactions and exfoliant dermatitis occurred at least twice as frequently in combination therapy compared to clindamycin monotherapy.[36] Irritancy index scores of benzoyl peroxide, clindamycin and combination therapy showed the highest score with benzoyl peroxide in comparison to clindamycin monotherapy and combination therapy ($P \leq 0.01$).[51] Another study investigating patient satisfaction with clindamycin/benzoyl peroxide gel in 257 patients illustrated that the most common side effects with combination treatment were dry skin and skin irritation. No serious events were reported.[52]

A recent pilot study[53] investigated two gel formulations of 1% clindamycin/5% benzoyl peroxide, with and without hydrating components (dimethicone and glycerin), in twenty acne vulgaris patients. Both formulations were successful in treating inflammatory and noninflammatory acne lesions. However the

addition of hydrating components resulted in a greater patient satisfaction and tolerance, as well as a higher and more consistent reduction in inflammatory lesions after 12 weeks.

### Clindamycin/retinoid versus monotherapy

In comparing clindamycin/tretinoin gel to clindamycin lotion, 24% and 19% of patients respectively reported an adverse event. More patients in the clindamycin/tretinoin group complained of erythema and skin desquamation after 12 weeks than in the clindamycin monotherapy group ($P = 0.027$, $P = 0.007$ respectively).[41]

Another study examining clindamycin/adapalene to clindamycin/vehicle, showed that both groups experienced adverse events (30.4%, 21.8% respectively), with most events being mild or moderate. A statistical significance was reached in patients with moderate to severe irritation in scaling ($P < 0.05$), dryness ($P < 0.01$) and stinging/burning ($P < 0.05$) in the adapalene/clindamycin group in comparison to the clindamycin/vehicle group, but were generally mild in nature.[40]

A large study evaluated the tolerability of clindamycin phosphate 1.2%/tretinoin 0.025% in two cohorts of 442 mild-severe acne patients for up to 52 weeks. The combination therapy of clindamycin/tretinoin was well tolerated. 92% of patients reported no itching, 91% with no burning and 94% reported no stinging. The most common adverse events were mild in nature and included a flare of acne in 7%, sunburn in 3%, hypersensitivity and contact dermatitis in 2% and 1% respectively, and desquamation at the application site in 1% of patients.[54]

## Place in Therapy

Topical antimicrobials are common first line treatment options in mild to moderate acne patients.[55] Consensus at the Global Alliance to Improve Outcomes in Acne showed that patients with inflammatory lesions receive the greatest benefit from combination therapy (topical antimicrobial/retinoid or topical antibiotic/benzoyl peroxide). Treatment with combination products allows for more steps in the pathogenicity of acne to be targeted. Topical retinoid/antimicrobial therapy have been shown to clear inflammatory and noninflammatory acne lesions quicker and more efficiently than with antimicrobial monotherapy.

Also it is believed that retinoids allow for a better penetration of the topical antimicrobial, resulting in a quicker time to improvement. When clearing is reached, the topical antimicrobial can be stopped and maintenance therapy with the topical retinoid is continued. Topical antibiotic/benzoyl peroxide reduces the risk of developing resistant *Propionibacterium acnes* strains.[14]

The many studies cited here demonstrate the ability of clindamycin monotherapy to achieve a statistically significant reduction in inflammatory and total lesion counts in comparison to vehicle. However combination therapy with benzoyl peroxide or a topical retinoid illustrated a higher efficacy in acne clearance through a statistically significant reduction in all lesion counts. Clindamycin/benzoyl peroxide also resulted in the highest reduction of *P. acnes* and the lowest rate of resistant organisms.

As mentioned above (pharmacology-side effects and patient preference sections), topical clindamycin is a relatively safe drug used in the management of acne vulgaris. The formulation of clindamycin should be matched to the patient's skin type; gel and solution forms work well with oily skin types, and lotions work best for normal skin types. The most common adverse events are erythema, peeling, itching, dryness and burning.[14,56] When combined with benzoyl peroxide, common drug reactions include erythema and scaling, along with bleaching of clothes, linens and hair; less common adverse events include burning, acne flares and photosensitivity.[57] Typical adverse drug reactions with topical retinoids include erythema and scaling and to a lesser degree burning, acne flare ups and photosensitivity.[57] However most sources site these adverse reactions as mild to moderate in intensity and transient in nature.

Patients should be advised that acne improvement and clearance takes time and patient compliance. One source sites a 40% acne improvement after 8 weeks of therapy.[57] Treatment with any topical antibiotic typically lasts for at least 3 to 6 weeks.[14] Recommended treatments for mild inflammatory acne include a topical antibiotic applied twice daily for 2–4 weeks, or topical benzoyl peroxide or a combination of the two therapies. The antibiotic should slowly be tapered when no new acne lesion arise. For patients with a predominance of moderate to moderately severe inflammatory acne, recommended treatments

include a topical retinoid along with topical or systemic antibiotics.[58]

## Future Drugs in the Treatment of Acne Vulgaris

Therapies such as taurine bromamine, Zileuton, ectopeptidase inhibitors, honokiol and magnolol have the potential to become possible treatment options in acne vulgaris patients. Taurine bromamine is a haloamine made from activated neutrophils and eosinophils in the presence of inflammation, and possesses anti-inflammatory, anti-oxidant and antimicrobial properties.[59] A recent double-blind, randomized study compared topical taurine bromamine cream to 1% clindamycin gel in mild to moderate inflammatory acne patients for 6 weeks. Results showed a similar reduction in acne lesions with both treatments, as well as no reported adverse events with either treatment.[60]

Secondly, Zileuton impedes the activity of 5-lipoxygenase, an enzyme important in the production of leukotriene $B_4$, (an important molecule in the production of tissue inflammation). Zileuton is another possible future therapy for acne vulgaris, as in vitro human sebocytes were found to contain enzymes of the leukotriene pathway.

Clinical studies demonstrate Zileuton as being safe and effective. In a pilot study of 10 patients with moderate inflammatory acne, Zileuton was given $4 \times 600$ mg/day by mouth for 3 months. After 12 weeks, inflammatory lesions were reduced by a mean of 71% ($P = 0.007$), and noninflammatory lesions showed a 36% mean reduction ($P = 0.09$); a 65% mean reduction was found in total sebum lipids ($P = 0.04$), a 78% mean reduction in free fatty acids (not significant) and a 74% reduction in hydroperoxides (not significant) was also shown. Interestingly, a correlation between the reduction of inflammatory lesions to total serum lipids and free fatty acids in sebum ($P < 0.001$) was found. Thus Zileuton was shown to have anti-inflammatory properties, along with a reduction in lipids.[61,62]

In addition, the ectopeptidase inhibitors (inhibitors of dipeptidyl peptidase IV [DP IV] and aminopeptidase N [APN]) also show therapeutic promise in the treatment of acne vulgaris. A recent in-vitro study demonstrated that DPV IV and APN are expressed on human sebocytes. Inhibitors of DPV IV and APN have been shown to not only target the hyper proliferation of sebocytes and keratinocytes, but also exhibit anti-inflammatory effects through an upregulation in the IL-1 receptor antagonist in both sebocytes and keratinocytes.[63]

Lastly, honokiol and magnolol, two important phenolic components from the stem bark of *Magnolia* sp, are also being considered for future acne treatments. In an in-vitro study, honokiol and magnolol were found to have antibacterial properties against *Propionibacterium acnes* and *Propionibacterium granulosum* as well as anti-inflammatory activities, as seen through a decrease by *P. acnes* in the secretion of interleukin-8 and tumor necrosis factor alpha. A human skin primary irritation test was conducted, which showed no adverse reactions with either compound when applied topically.[64] However more clinical studies are needed to fully assess the effectiveness and safety of all of the above listed future acne treatments.

## Conclusions

Topical clindamycin is a safe and effective treatment in mild to moderately severe inflammatory acne vulgaris. It is a highly tolerable antimicrobial, with the most common side effects being mild and transient in nature. Combination treatments with benzoyl peroxide or a topical retinoid offer the most favorable outcomes in decreasing acne severity, treatment duration, as well as bacterial resistance.

## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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