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REVIEW ARTICLE

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Topical clindamycin for acne vulgaris: analysis of gastrointestinal events

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ABSTRACT

Purpose: Topical clindamycin, a lincosamide antibiotic, is commonly combined with benzoyl peroxide or a retinoid for acne vulgaris (AV) treatment. While oral and topical clindamycin carry warnings/contraindications regarding gastrointestinal (GI) adverse events (AEs), real-world incidence of GI AEs with topical clindamycin is unknown. This review provides background information and an overview of safety data of topical clindamycin for treating AV.

Materials and Methods: Available safety data from published literature, previously unpublished worldwide pharmacovigilance data, and two retrospective cohort studies were reviewed.

Results and Conclusions: According to pharmacovigilance data, the rate of GI adverse drug reactions with topical clindamycin-containing products was 0.000045% (64/141,084,533). Results from two retrospective medical record studies of patients with AV indicated that physicians prescribe topical clindamycin equally to patients with or without inflammatory bowel disease history, and that rates of pseudomembranous colitis in these patients were low. In 8 published pivotal clinical trials of topical clindamycin for AV, GI AEs were reported in 1.4% of participants. Limitations include under/inaccurate reporting of AEs or prescription data and limited generalizability. This review of published case reports, worldwide pharmacovigilance data, retrospective US prescription data, and clinical trials safety data demonstrates that the incidence of colitis in patients exposed to topical clindamycin is extremely low.

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Clindamycin; topical; acne vulgaris; adverse events; colitis; inflammatory bowel disease

Introduction

Clindamycin, a lincosamide antibiotic (1), was synthesized in 1966 (2) and first approved in the United States (US) as a topical formulation for treatment of acne vulgaris (AV) in 1980 (3). Oral or topical formulations can be used for AV treatment (3), though orals are more limited for this indication, and monotherapy with topicals or orals is not recommended due to the frequent emergence of bacterial resistance (4). Topical clindamycin for AV treatment in the US is available as a lotion, gel, solution, or foam (1%–2% concentration) (5–8).

Oral clindamycin carries warnings and contraindications regarding the development of gastrointestinal (GI) adverse events (AEs) including *Clostridioides difficile* (formerly known as *Clostridium difficile*; *C. difficile*) colitis (9). While topical formulations have similar warnings and contraindications (6–8), the real-world incidence of these AEs is unknown. This review provides background information on oral and topical clindamycin for AV treatment. Available safety data from published literature, previously unpublished pharmacovigilance data, and two retrospective cohort studies are reviewed, with a focus on GI AEs following topical administration.

Mechanism of action

Clindamycin inhibits bacterial protein biosynthesis through irreversible binding to the 50S subunit of the bacterial ribosome (10). It is effective against aerobic Gram-positive cocci and anaerobic Gram-negative bacilli, has some efficacy in treating methicillin-resistant *Staphylococcus aureus* in skin and soft tissue infections, and is efficacious against certain protozoa (9,11).

Use in acne vulgaris treatment

AV pathogenesis is a multifactorial process involving increased sebum production, abnormal follicular keratinization, multiple inflammation pathways, and *Cutibacterium acnes* (*C. acnes*) proliferation (4). Clindamycin reduces *C. acnes* proliferation and exhibits multiple anti-inflammatory properties (1). though correlation of the latter with AV therapeutic outcomes warrants further evaluation. The most recent treatment guidelines recommend treating mild-to-moderate AV with monotherapy consisting of topical benzoyl peroxide (BPO) or a topical retinoid, or a combination of topical BPO with a topical retinoid and/or a topical or oral antibiotic (4). This reflects overall what is believed to occur with real-world US prescribing for AV. It is recommended that oral or topical antibiotics be combined with BPO or a topical retinoid to improve the efficacy of topical antibiotic therapy, mitigate bacterial resistance where both BPO and the topical antibiotic are applied, and optimize AV control following oral treatment cessation (4). A metanalysis has demonstrated that for mild-to-moderate/moderate-to-severe

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AV, topical treatments combining clindamycin and BPO or a retinoid were some of the most effective treatments (12). A criticism of clindamycin-retinoid formulations is the lack of BPO to mitigate bacterial resistance; however, efficacy was demonstrated with short-term and long-term studies (3–52 weeks) (13–18).

Pharmacokinetics

Peak serum levels after topical, oral, intramuscular (IM), or intravenous (IV) administration of clindamycin are shown in Table S1. Systemic exposure is lower with topical clindamycin (range: 2%–8% bioavailability (19,20)) than with oral or IV formulations (~90% bioavailability (9,21)) but varies greatly depending on the clindamycin salt (e.g., ester, phosphate, hydrochloride), how it is solubilized, and vehicle formulation characteristics (20,22,23). Urinary excretion is also lower with topical (<1% (6,7,19,20)) versus oral and IV clindamycin formulations (10%–13%, both (9,20)). The lower systemic exposure observed with topical formulations of clindamycin would be expected to decrease the risk of AEs and systemic effects (24,25).

Gastrointestinal safety and resistance

While topical clindamycin has a more favorable safety and tolerability profile than oral formulations, the possible development of antibiotic resistance or colitis are potential limitations (Table 1) (6–9). Antibiotic resistance is a major concern with any antibiotic, and both oral and topical clindamycin are associated with the development of resistance (26). Several countries have reported >50% of *C. acnes* strains as resistant to certain antibiotics such as macrolides and clindamycin (5,26,27). Combining topical clindamycin with topical BPO reduces the development of resistant bacterial strains and improves efficacy (4,28–31).

Another issue with many systemic antibiotics, including oral clindamycin, cephalosporins, and fluroquinolones, is that they can alter the diversity and density of intestinal bacterial species, possibly for as long as several months and up to two years after treatment (9,32,33). This altered environment may allow colonization of *C. difficile*, which produces toxins that can cause intestinal inflammation and epithelial damage (32). Signs and symptoms of infection range from mild diarrhea to potentially fatal pseudomembranous colitis or toxic megacolon (33). These infections can be resistant to antimicrobials and may require colon removal (9).

Clindamycin and colitis/intestinal microflora

Due to the association with pseudomembranous or *C. difficile* colitis, oral clindamycin should be prescribed with caution in patients with a history of colitis or GI disease (Table 1) (9). Though the association with topical clindamycin formulations is less clear (24). FDA labels contraindicate it in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis (6–8). Two randomized, double-blind, vehicle-controlled studies in patients with AV showed mixed results regarding topical clindamycin-induced intestinal microflora alterations (34,35). In one study of 19 patients, 4 had *C. difficile* detected in stool samples during treatment. However, there were no discernable levels of clindamycin in stool or urine samples and no significant alterations in intestinal microflora (35). In the second study ($n = 10$), there were no changes in intestinal microflora in patients treated with topical clindamycin, whereas pronounced changes occurred in patients treated with oral tetracycline (34). Neither study noted increased incidence of diarrhea or GI AEs with topical clindamycin (34,35).

Case reports of colitis with topical clindamycin

In a search of published articles indexed on PubMed®, there were 4 case reports of topical clindamycin-associated colitis (see

Table 1. Safety and antibiotic resistance of clindamycin from US prescribing information.

	Oral clindamycin (9)	Topical clindamycin (6,8)
Adverse events	*C. difficile*-associated diarrhea, abdominal pain, pseudomembranous colitis, esophagitis, nausea, vomiting, diarrhea; hypersensitivity reactions; skin pruritis, vaginitis, angioedema, rare instances of exfoliative dermatitis; liver function abnormalities/jaundice; transient leukopenia/eosinophilia; acute kidney injury; drug reaction with eosinophilia and systemic symptoms; polyarthritis	Dermatitis/contact dermatitis/fungal dermatitis, folliculitis, photosensitivity reaction, pruritus, headache, application site reaction/burning/pruritis/dryness; stinging; eye pain
Warnings/precautions	*C. difficile*-associated diarrhea; anaphylactic/severe hypersensitivity reactions; nephrotoxicity; should not be used to treat meningitis; should be reserved for serious infections where less toxic antimicrobial agents are inappropriate; use with caution in atopic patients; use with caution in patients with a history of colitis/gastrointestinal disease; test liver enzymes in patients with severe liver disease	*C. difficile*-associated disease; diarrhea, bloody diarrhea, colitis (may be severe/fatal), pseudomembranous colitis; skin irritation; use with caution in atopic patients
Contraindications	History of hypersensitivity to clindamycin or lincomycin	History of irritable bowel disease or antibiotic-associated colitis, including regional enteritis, pseudomembranous colitis/ulcerative colitis; history of hypersensitivity to clindamycin or lincomycin
Drug-drug-interactions	Neuromuscular blocking agents; cytochrome P450 3A4 and 3A5 inhibitors	Neuromuscular blocking agents; erythromycin-containing agents; aminoglycoside agents
Use in pregnancy	Teratogenic: should not be used in pregnancy unless clearly needed	Teratogenicity unknown: should not be used in pregnancy unless clearly needed
Antibiotic resistance	Macrolide-induced resistance to clindamycin has occurred in some isolates of macrolide-resistant bacteria; cross-resistance with lincomycin/lincosamides, macrolides and streptogramin B	Associated with the development of antimicrobial resistance in *C. acnes* and other bacteria (e.g., *Staphylococcus aureus*, *Streptococcus pyogenes*); cross-resistance with erythromycin

Note: C. acnes: *Cutibacterium acnes*; *C. difficile*: *Clostridioides difficile*; US: United States.

Supplementary Materials for full narratives) (36–39). Patients were aged 24, 26, 28, and 42 years, and were all using clindamycin for AV treatment. Two patients had positive tests for *C. difficile* and confirmed pseudomembranous colitis (36,37). The other two patients had diarrhea/loose stools that ceased upon discontinuation of clindamycin (38,39).

Pharmacovigilance data

Given the scarcity of peer-reviewed articles detailing safety events following real-world topical clindamycin use, worldwide pharmacovigilance data were gathered to determine the risk of GI AEs (reported as adverse drug reactions [ADRs]) and drug resistance with use of topical clindamycin as monotherapy or in fixed-dose combinations (see Supplementary Materials for methods). Only ADRs that were GI related (GI disorders and certain infection and infestation events [*C. difficile* or clostridial infection, colitis, GI infection, and pseudomembranous colitis]), or those noted as drug resistance were chosen from adverse reaction reports (Supplementary Materials for methods). These specific ADRs were chosen as they are noted in the US prescribing information of oral and topical clindamycin products (see Table 1) and may be a concern for physicians prescribing these drugs.

Estimated exposure to clindamycin-containing products

Estimated worldwide exposure (1 exposure = 1 tube/bottle) to topical clindamycin monotherapy was 7,276,046 exposures (time period covered: January 2007–October 2022). Exposure to topical clindamycin fixed-dose dyads was: 88,795,702 exposures to clindamycin and benzoyl peroxide (December 2008–December 2022), and 45,012,785 exposures to clindamycin and tretinoin (May 2012–May 2022). Specific clindamycin products and countries where marketed are noted in Table S2.

Table 2. Adverse drug reactions of interest from post-marketing data sources of 141,265,758 patients (1 January 1900–31 December 2022).

	Serious events	Non-serious events
GI disorders ($N=64$ patients)		
Abdominal[a]	5	21
Anal fissure	0	1
Colitis	3	7
Constipation	1	2
Diarrhea (includes hemorrhagic)	1	37
Dyspepsia	0	2
Flatulence	0	2
Frequent bowel movements	0	1
Hematochezia	1	1
Irritable bowel syndrome	0	2
Mucous in stools	0	1
Nausea	1	5
Proctalgia	1	0
Vomiting	1	7
Total events	14	89
Infections and infestations ($N=0$ patients)		
Clostridial infection	0	0
Clostridial colitis	0	0
C. difficile infection	0	0
C. difficile colitis	0	0
GI bacterial infection	0	0
GI infection	0	0
Pseudomembranous colitis	0	0
Total events	0	0
General disorders ($N=0$ cases)		
Drug resistance	0	0
Total events	0	0

Note: C. difficile: Clostridioides difficile; GI: gastrointestinal.
[a]Includes abdominal pain, pain upper, pain lower, discomfort, and distention.

Gastrointestinal events and resistance

Of the 141,084,533 estimated exposures to a topical clindamycin-containing product, GI-related ADRs were reported in 64 patients (0.000045%; time period: January 1, 1900–December 31, 2022; Table 2). All cases occurred in North America ($n=57$) and Europe ($n=7$). Patient median age was 26 years ($n=50$; range: 10–83 years), and most were female (42/60). The topical products noted were: 1 monad ($N=1$: clindamycin); 2 dyads ($N=59$: clindamycin/BPO [$n=35$]; clindamycin/tretinoin [$n=24$]); 1 triad ($N=1$: clindamycin/BPO/adapalene); and multiple ($N=3$: clindamycin/BPO and tretinoin [$n=1$]; clindamycin/BPO and metronidazole [$n=1$]; clindamycin/BPO, clindamycin/tretinoin, and doxycycline [$n=1$]).

In the 64 patients, a total of 103 GI-related ADRs were reported; of these 14 were serious and 89 were nonserious (Table 2). Notably, there were no cases of pseudomembranous/clostridial colitis or *C. difficile* infection/colitis. There were 10 non-clostridial colitis events in 9 patients (2 separate instances occurred in the same patient) and 2 patients with irritable bowel syndrome (IBS; Table 3). All patients with colitis were using combination clindamycin with BPO or tretinoin. Three patients had concomitant antibiotics other than clindamycin noted (route of administration not provided for all). Half of colitis events were considered unlikely/unknown in terms of their relation to treatment. Two patients had a previous medical history of colitis. Three events were considered serious. Of the two patients with IBS, both were using combination clindamycin treatment, neither event was considered serious, and both events were considered unlikely to be related to treatment. One patients was taking metronidazole for infection prophylaxis (Table 3).

Pharmacovigilance data also found no reported drug resistance events, although this ADR is difficult to capture without signs, symptoms, or testing for resistance.

These worldwide pharmacovigilance data show that of the estimated hundreds of millions of exposures to topical clindamycin treatments, rates of GI ADRs including colitis or IBS were 0.000045% and no cases of *C. difficile* infection/colitis or drug resistance were reported. The analyses were limited in part by the assumption that one exposure equals one tube/bottle. Further, as AV is a chronic condition, it is likely a single patient would have had multiple exposures over time. While it is not possible to accurately calculate the percentage of clindamycin-treated patients who experienced a GI ADR using world-wide pharmacovigilance data, the rate of reported GI ADRs would only be 0.004% given the following more conversative assumptions: all 141,084,533 exposures were due to 1,567,606 patients who received one bottle/tube every two months for 15 consecutive years. While there are also limitations inherent to spontaneous reporting systems data (e.g., delays between use of a drug and detection of related ADRs, underreporting of ADRs, and missing or duplicated reports (40)), no safety signals for GI-related-ADRs were observed in this analysis of topical clindamycin.

Retrospective data

In a published retrospective study of patients receiving prescriptions for antibiotics during the years 1977–1980, there were no colitis reports from any of the 1124 patients estimated to have received topical clindamycin prescriptions (41). It was not noted if the prescriptions were for AV.

Table 3. Colitis and IBS events in patients using topical clindamycin (January 1900–December 2022).

Event	Drug	Indication	Event severity	Relation to drug	Concomitant antibiotics	Other concomitant medications
Colitis	Clindamycin/BPO	Acne	Serious	Unlikely	Clarithromycin; topical erythromycin/BPO; minocycline; topical clindamycin phosphate (2 formulations); topical sodium sulfacetamide	Topical adapalene; topical BPO
Colitis	Clindamycin/BPO	Acne	Serious	Unlikely[a]	NR	NR
Colitis	Clindamycin/tretinoin	Papule	Serious	Unlikely	NR	Levothyroxine sodium; levonorgestrel/ethinyl estradiol
Colitis	Clindamycin/BPO	Cystic acne	Non-serious	Highly probable	Minocycline hydrochloride	NR
Colitis	Clindamycin/BPO	Folliculitis[b]	Non-serious	Possible	NR	NR
Colitis	Clindamycin/BPO	Acne	Non-serious	Possible[a]	NR	Topical tretinoin; vitamins E and B; magnesium; norethisterone acetate/ethinyl estradiol; valsartan
Colitis	Clindamycin/BPO	Acne	Non-serious	Possible	Possible oral antibiotic[c]	NR
Colitis	Clindamycin/tretinoin	Acne	Non-serious	Possible	NR	NR
Colitis	Clindamycin/BPO[d]	Acne	Non-serious (2 events)	Unknown (2)	NR	NR
IBS	Clindamycin/BPO	Acne	Non-serious	Unlikely	NR	Cystic fibrosis medications[c]; diabetes medications[c]
IBS	Clindamycin/BPO + metronidazole	Acne; infection prophylaxis	Non-serious	Unlikely	Metronidazole	NR

Note: BPO: benzoyl peroxide; IBS: irritable bowel syndrome; NR: not reported.
[a]Patient had previous medical history of colitis.
[b]Noted as an unapproved indication.
[c]Drug(s) not specified.
[d]Two separate instances reported in the same patient.

Table 4. Acne vulgaris patients with or without IBD prescribed topical clindamycin within one year of first acne vulgaris diagnosis (1 January 2011–31 January 2019).

IBD history	Total patients	Patients prescribed topical clindamycin, n (%)
None	70,151	14,495 (20.7%)
IBD[a]	515	98 (19.0%)
Crohn's disease	301	55 (18.3%)
Ulcerative colitis	262	52 (19.8%)

Note: IBD: inflammatory bowel disease (Crohn's or ulcerative colitis). Demographic characteristics: patients without IBD: mean age 32.7 years, 72% females, 80% White; patients with IBD: mean age 40.1 years, 67% females, 85% White.
[a]Some patients had diagnoses for both Crohn's disease and ulcerative colitis.

As there is little published retrospective data on this topic, we carried out two retrospective cohort studies using the IBM Explorys database, comprising electronic medical record data from >40 healthcare delivery networks and 53 million US patients (42) (see Supplemental Materials for methods). One study examined frequency of topical clindamycin monotherapy or combination prescriptions in patients with AV, with or without a history of IBD (inflammatory bowel disease; i.e., Crohn's disease or ulcerative colitis). Of the 70,666 eligible patients with AV, 515 had an IBD diagnosis (Table 4). Prescriptions of topical clindamycin in the past year did not significantly differ between patients with or without IBD (19.0% vs 20.7%; Table 4).

The second study analyzed incidence of pseudomembranous colitis diagnoses within 30 days of an initial prescription for topical clindamycin monotherapy or combination, topical tretinoin monotherapy, and systemic clindamycin monotherapy or combination in patients with AV. To minimize the chances of including unrelated AEs, only those occurring within one month following the initial clindamycin prescription were analyzed. A total of 28,422 patients were identified. IBD history was <2% in any treatment group (Table 5). There were 3 incident cases of pseudomembranous colitis; none had a history of IBD (Table 5). Of these 3 cases, 0 were identified in 5977 patients receiving topical clindamycin monotherapy, 2/12,001 (0.02%) in patients receiving topical clindamycin + tretinoin *or* benzoyl peroxide, and 1/34 (2.9%) in a patient receiving topical clindamycin + oral clindamycin.

Data from these retrospective studies indicate that rates of colitis/pseudomembranous colitis among patients with AV prescribed topical clindamycin are low. These studies also show that physicians prescribe clindamycin for AV treatment equally to patients with or without a history of IBD, regardless of warnings and contraindications noted in the prescribing information (Table 1). This demonstrates the disconnect that can occur between the initial FDA-approved product labeling and current medical community understanding of what is believed to be true regarding a drug's safety, especially as approved labeling is not automatically updated.

These retrospective analyses were conducted using claims data in patients with AV, which may limit generalizability of the results. Other limitations include AE underreporting and lack of information regarding whether prescriptions were filled and how much was used. Finally, there was no control for other prescriptions known to be associated with GI AEs (e.g., non-clindamycin oral antibiotics, etc). Recognizing these limitations, a safety signal for topical clindamycin was not demonstrated for colitis or pseudomembranous colitis.

Clinical trials data

Safety data for GI-related AEs were gathered from published articles indexed on PubMed® or from US FDA New Drug Applications (3) of pivotal clinical studies of topical clindamycin (monad, dyad, or triad formulations) for AV. Thirteen phase 3 studies were found (13,43–48); 1 phase 2 study was included as it had been pooled with the phase 3 study (47). Of these, 8 studies provided safety data ($N = 4319$) (44–48).

Table 5. Incidence of pseudomembranous colitis within 30 days of initial prescription for acne vulgaris treatment.

Treatment	Total patients	IBD history, n (%)	Pseudomembranous colitis diagnosis[a], n (%)	95% CI	Incidence[b] (95% CI)
Topical monotherapy					
Clindamycin	5977	66 (1.1%)	0 (0%)	0, 0.06	0 (0, 0.6)
Tretinoin	10,307	93 (0.90%)	0 (0%)	0, 0.04	0 (0, 0.4)
Topical combination					
Clindamycin + tretinoin OR benzoyl peroxide	12,001	94 (0.78%)	2 (0.02%)[d]	0.005, 0.06	0.2 (0.05, 0.6)
Systemic monotherapy					
Clindamycin	84	1 (1.2%)	0 (0%)	0, 4.4[c]	0 (0, 44)[c]
Systemic + topical					
Clindamycin + clindamycin	34	0 (0%)	1 (2.9%)[d]	0.5, 14.9[c]	29 (5, 149)[c]
Clindamycin + tretinoin	19	0 (0%)	0 (0%)	0, 16.8[c]	0 (0, 168)[c]

Note: CI: confidence interval; IBD: inflammatory bowel disease (Crohn's or ulcerative colitis). Patient demographic characteristics: range: mean age 25–33 years, 65%–78% females, 70%–77% White.
[a]Within the past 30 days.
[b]Per 1000 patients.
[c]Estimates based on small sample sizes are imprecise and should be interpreted with caution.
[d]No history of IBD.

A total of 2672 participants (safety populations) with AV were treated once daily for 10–12 weeks with a topical containing clindamycin phosphate alone, combined with BPO (2.5%–5%) or tretinoin (0.025%), or combined with adapalene (0.15%) and BPO (3.1%). GI-related AEs were reported in up to 1.4% of participants (38/2672). In 2 studies that reported severity (45,48), 3 AEs were mild (diarrhea $n=1$; abdominal pain, $n=1$; hematochezia, $n=1$) and 1 severe (diarrhea, $n=1$). Overall, GI AEs in clinical trials of clindamycin-containing topical treatments for AV were low and similar to comparators (Table S5).

Conclusions

Topical clindamycin is a commonly prescribed antibiotic that, when combined with topical benzoyl peroxide or a topical retinoid, is used to treat AV. Oral clindamycin carries warnings and contraindications regarding development of pseudomembranous or *C. difficile* colitis. While topical formulations have similar warnings and contraindications, a review of published case reports, worldwide pharmacovigilance data, retrospective US prescription data, and clinical trials safety data demonstrate that the incidence of colitis/pseudomembranous colitis in patients exposed to topical clindamycin is extremely low. With similar rates of prescriptions in patients with or without a history of IBD, providers do not appear concerned whether patients have IBD or may be unaware of warnings in FDA-approved labeling (i.e., package insert) when prescribing topical clindamycin. Given the data contained in this review, the strict warnings around colitis and IBD in the prescribing information for topical clindamycin-containing products appear to be overstated and warrant a critical reevaluation. This has significant implications as third-party payers may choose not to cover the cost of topical clindamycin prescribed for AV patients with IBD even when physicians have carefully weighed the risks and benefits with these patients. Additionally, clinicians may be unduly exposed to potential medicolegal risks from old warnings in FDA-approved labeling that are exaggerated based on currently available data and have not been formally reevaluated.

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Author contributions

All authors made substantial contributions to the conception or design of the work; drafted the work/revised it critically; approved the version to be published; and agree to be accountable for all aspects of the work.

Disclosure statement

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Data availability statement

The data that support the findings of this study are available from the corresponding author, GH, upon reasonable request.

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