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Oral Antibacterial Therapy for Acne Vulgaris

An Evidence-Based Review

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Abstract and Introduction

Abstract

Background To some degree, acne vulgaris affects nearly every individual worldwide. Oral antibiotic therapy is routinely prescribed for the treatment of moderate to severe inflammatory acne; however, long-term use of oral antibiotics for acne may have unintended consequences.

Objective The aim of this study was to provide a systematic evaluation of the scientific evidence on the efficacy and appropriate use of oral antibiotics in the treatment of acne.

Methods A systematic search of MEDLINE was conducted to identify randomized controlled clinical trials, systematic reviews, and meta-analyses evaluating the efficacy of oral antibiotics for acne. Overall, 41 articles that examined oral antibiotics compared with placebo, another oral therapy, topical therapy, alternate dose, or duration were included in this study.

Results Tetracyclines, macrolides, and trimethoprim/sulfamethoxazole are effective and safe in the treatment of moderate to severe inflammatory acne. Superior efficacy of one type or class of antibiotic could not be determined, therefore the choice of antibiotic is generally based on the side-effect profile. Although different dosing regimens have been studied, there is a lack of standardized comparator trials to determine optimal dosing and duration of each oral antibiotic used in acne. The combination of oral antibiotics with a topical therapy is superior to oral antibiotics alone.

Conclusion This article provides a systematic evaluation of the scientific evidence of the efficacy of oral antibiotics for acne. Due to heterogeneity in the design of the trials, there is insufficient evidence to support one type, dose, or duration of oral antibiotic over another in terms of efficacy; however, due to increasing resistance to antibiotics, dermatologists should heed consensus guidelines for their appropriate use.

Introduction

Acne vulgaris is the eighth most prevalent disease worldwide. Almost every individual between 15 and 17 years of age is affected.[1,2] Acne may be associated with lasting side effects, including facial scars, feelings of low self-esteem, and depression.[3]

Several independent, interacting factors contribute to acne pathogenesis, including increased sebum production, increased keratinization of the follicular epithelium, inflammation, and overgrowth of normal skin microflora, particularly Gram-positive *Propionibacterium acnes*.[4–6] These factors are inter-related and synergistic; therefore, it is difficult to tease out the primary or initiating process. Sebum, the nutrient source of *P. acnes*, is necessary for acne development.[5] In turn, *P. acnes*, relying on sebum, forms biofilms in sebaceous sites, which promotes follicular hyperkeratinization and stimulates the host inflammatory response.[6,7] The resulting inflammation leads to follicular wall rupture, and the downstream inflammatory response stimulates further tissue destruction and scar formation.[6] In addition, increased follicular keratinization promotes even more proliferation of *P. acnes*, creating a complex cycle.[4]

Acne therapies include topical and systemic treatments, targeting different aspects of acne pathogenesis. Oral antibiotics are routinely prescribed for the treatment of moderate–severe inflammatory acne and are believed to be successful because they target both the bacteria and associated inflammation. The antibiotics used in the treatment of acne include tetracyclines, macrolides, clindamycin, and trimethoprim/sulfamethoxazole. However, despite their efficacy, prolonged use of oral antibiotics may potentially alter the skin and gut microbiome and contribute to antibiotic resistance, a growing global concern. The aim of this review was to critically evaluate the published literature on the role of oral antibiotics in the treatment of acne, as well as the specific classes, doses, and duration of treatment.

Methods

A MEDLINE search was conducted to identify randomized controlled trials, systematic reviews, and meta-analyses that evaluated oral antibiotic therapy for acne. Only peer-reviewed articles published in English prior to 30 September 2016 were considered for inclusion. The search terms 'acne (vulgaris)', 'oral antibiotics', 'tetracycline', 'doxycycline', 'minocycline', 'macrolides', 'erythromycin', 'azithromycin', 'trimethoprim', 'trimethoprim/sulfamethoxazole', and 'clinical trial' were used, and 543 articles were identified. After titles and abstracts were screened for relevance, a total of 50 full-text publications were reviewed for content. Only articles evaluating oral antibiotics compared with another oral therapy, topical therapy, placebo, or alternate dose or duration were considered. Twenty-eight full-text articles were identified that fulfilled these criteria, with a further cross-reference of bibliographies identifying an additional 13 articles (Fig. 1). The identified studies were evaluated using the Strength of Recommendation Taxonomy (SORT) 3-point grading scale.[8] Finally, the most up-to-date consensus guidelines for acne treatment from expert committees were reviewed for their recommendations.

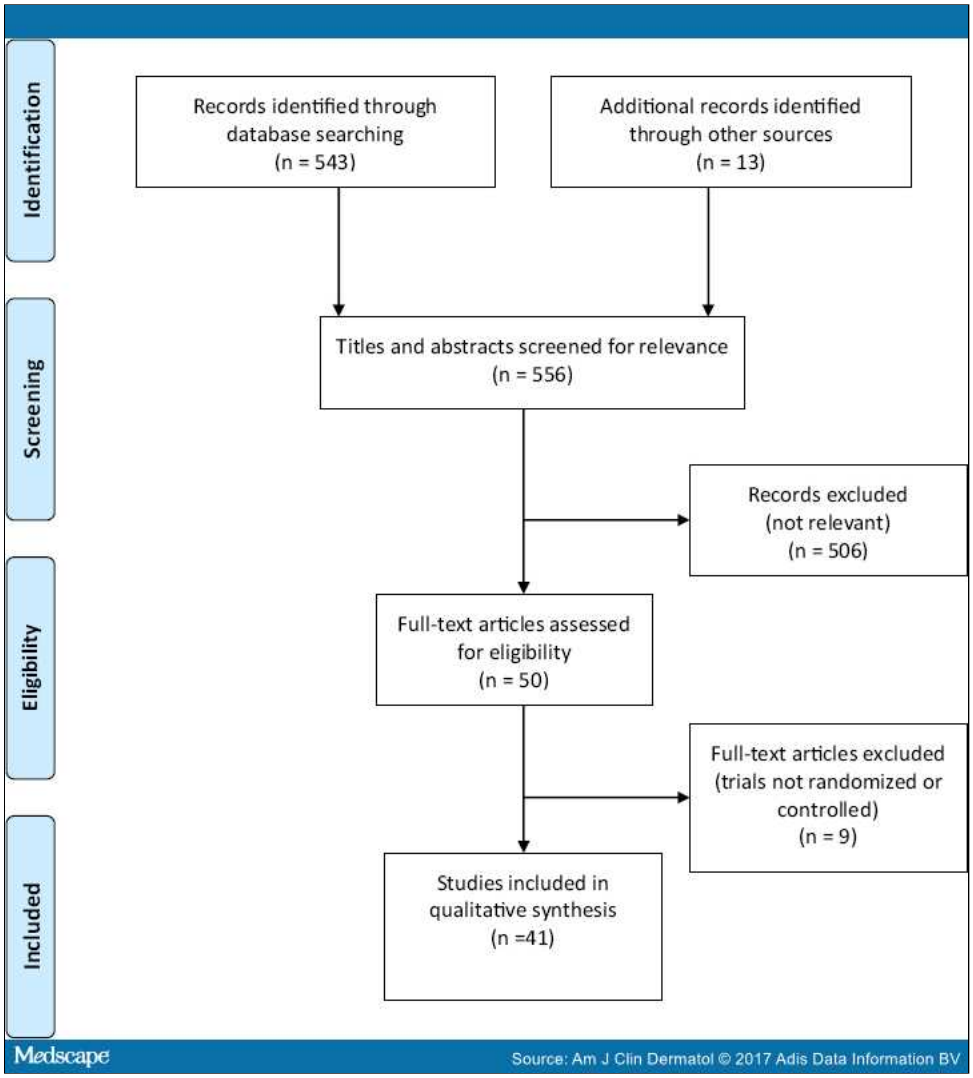

Figure 1.

Identification and selection of studies

Results

Guidelines

Several consensus acne treatment guidelines have been published; summaries of eight consensus guidelines from separate expert committees are included in . Five guidelines report that oral antibiotics are appropriate in moderate–severe inflammatory acne;[3,9–12] one recommends use in widespread mild–severe inflammatory acne or moderate nodular/conglobate acne;[13] and one recommends the use of oral antibiotics only in nodular acne.[14]

Table 1. Consensus guidelines for oral antibiotic use in the treatment of acne vulgaris

Study (year)	Committee	Type of acne (for oral antibiotics)	Treatment recommendation	Dosage	Duration
Zaenglein et al. (2016) [3]	The American Academy of Dermatology	Moderate to severe inflammatory acne resistant to topical therapy	Evidence supports the use of tetracyclines, macrolides, TMP/SMX, trimethoprim, amoxicillin, and cephalexin for acne. The tetracycline class is recommended first-line unless contraindicated. Restrict the use of erythromycin because of its increased risk of bacterial resistance. Oral antibiotic monotherapy is discouraged; instead, concomitant use of oral antibiotics with topical retinoids or retinoid/BP is recommended. Maintenance therapy with topical therapies after oral antibiotics is recommended	Minocycline ER at 1 mg/kg is safest, but no evidence that it is more efficacious. Doxycycline effective between the 1.7 and 2.4 mg/kg range. SDD of 20 mg bid or 40 mg daily	Simultaneous use with topical retinoid or retinoid/BP for 3–4 months. If alternative therapies are inappropriate, a longer duration is acceptable with consistent follow- up and re-evaluations
Thiboutot	The Global	Moderate to	A topical retinoid and antimicrobial therapy should be	Tetracycline: 500 mg	Clinical effect

et al. (2009) [9] [updated from Gollnick et al. (2003) [15]]	Alliance to Improve Outcomes in Acne (2009 updates from 2003)	severe inflammatory acne	tried before initiating oral antibiotics. Tetracyclines, macrolides, and trimethoprim are effective for acne. Cephalosporins, fluoroquinolones, aminoglycosides, chloramphenicol, sulfonamides, and gyrase inhibitors should NOT routinely be used for acne because of lack of efficacy and safety considerations. Oral antibiotics should not be used as monotherapy; combination therapy of oral antibiotics and topical retinoids is recommended to clear inflammatory lesions and comedones faster than antibiotic therapy alone. Therefore, topical retinoids should be started at the initiation of antibiotic therapy. Use a topical retinoid for maintenance therapy for continued success. If retreatment is necessary, the same antibiotic should be used if it were effective, otherwise use an alternative antibiotic	bid; doxycycline: 50–100 mg bid; lymecycline: 150–300 mg daily; minocycline: 50–100 mg bid; erythromycin: 500 mg bid; TMP/SMX: 800 SMX/160 TMP; trimethoprim: 300 mg bid	takes approximately 4–8 weeks. The ideal duration is 3 months; minimum duration 6–8 weeks, maximum duration 12–18 weeks. Antibiotics should be tapered or discontinued when inflammatory lesions adequately resolve. If it is not possible to discontinue antibiotics, switch to a combination product with BP at 2 months
Dreno et al. (2004) [16]	European Expert Group on Oral Antibiotics in Acne	Not addressed	Tetracyclines, macrolides, clindamycin, trimethoprim, cotrimoxazole, and quinolones are all effective in acne. Tetracyclines should be used as first-line over other classes of antibiotics; second-generation tetracycline should be used before first-generation tetracycline; lymecycline and doxycycline should be used before minocycline based on safety profile. Oral antibiotic monotherapy is discouraged; a topical retinoid should always be prescribed with oral antibiotics. When oral antibiotics are used for prolonged periods of time (over 3 months), BP should be added to the regimen. Oral antibiotics should not be administered with topical antibiotics. Maintenance therapy should be with a topical retinoid ± BP. If retreatment is necessary, use the same antibiotic as the prior course	Lymecycline: 300–600 mg daily; minocycline/doxycycline: 100–200 mg daily; tetracycline: 1 mg daily	3 months' duration is recommended, but longer duration may be used until clinical improvement is achieved. Maximum duration: 6 months
Eichenfield et al. (2013) [10]	The American Acne and Rosacea Society convened a panel of pediatric dermatologists, pediatricians, and dermatologists (Endorsed by The American Academy of Pediatrics)	Moderate to severe inflammatory acne	In children older than 8 years of age, tetracycline, doxycycline, and minocycline are commonly used in the treatment of acne. In children under 8 years of age, erythromycin, azithromycin, and TMP/SMX may be used with caution. Erythromycin use is limited secondary to increased resistance. Avoid antibiotic monotherapy; combine with topical retinoid ± BP. If retreatment is necessary, use the same antibiotic as the prior course	Doxycycline: 50–100 mg daily or bid; tetracycline: 500 mg bid; minocycline: 50–100 mg daily or bid; minocycline ER: 1 mg/kg daily; erythromycin: 250–500 mg daily or bid; TMP/SMX: 160–800 mg bid	Discontinue or taper within 1–2 months, once new inflammatory lesions have stopped emerging
Goh et al. (2015) [11]	South-East Asia Study Alliance	Moderate to severe acne	Moderate acne: oral antibiotics, such as doxycycline, minocycline, lymecycline, or erythromycin combined with a topical retinoid and topical BP. Severe acne: 6–8 weeks of recommended regimen for moderate acne; if no response is seen, then oral isotretinoin is recommended. Oral antibiotics should never be administered as monotherapy or with topical antibiotics	Doxycycline: 100–200 mg/day; tetracycline: 500–1000 mg/day; minocycline 100–200 mg/day; lymecycline: 300–600 mg/day; erythromycin: 500–1000 mg/day	Minimum: 6 weeks
Nast et al. (2012) [13]	Experts officially nominated by	Widespread mild to moderate papulopustular	Oral antibiotics should be reserved for more widespread disease. Systemic treatment should always be combined with a topical retinoid ± BP.	Not addressed	Not addressed

	the European Dermatology Forum or the European Academy of Dermatology and Venereology	acne, severe papulopustular, or moderate nodular/conglobate acne	Doxycycline and lymecycline should be chosen before minocycline or tetracycline		
Gollnick et al. (2016) [12]	17 acne experts reviewing the guidelines from the Global Alliance, European Dermatology Forum, American Academy of Dermatology, and groups from Asia	Moderate to severe predominantly papulopustular acne	Oral antibiotic treatment should be initiated with fixed combination adapalene 0.1%/BP 2.5%; if a response is seen, continue treatment for at least 12 weeks. When cleared/almost cleared, use topical retinoid for maintenance. If no response, check compliance and consider changing the oral agent	Not addressed	Not addressed
Abad-Casintahan et al. (2011) [14]	Asian Working Group	Nodular acne	The preferred oral antibiotics are tetracyclines and macrolides. Oral antibiotics should always be used with a topical retinoid therapy. BP should be added to the regimen if the duration of oral antibiotics exceeds 8–12 weeks. Second-line treatment for non-responders or patients who cannot tolerate therapy is oral isotretinoin	Not addressed	Limited to 12 weeks when possible

bid twice daily, *BP* benzoyl peroxide, *ER* extended release, *SDD* submicrobial dose doxycycline, *TMP/SMX* trimethoprim/sulfamethoxazole

All of the guidelines recommend the combination of oral antibiotics with a topical retinoid, and possibly benzoyl peroxide, and also recommend combination therapy because it targets multiple pathophysiological mechanisms,[15] achieves faster, more complete resolution of comedonal and inflammatory lesions,[13] and combats the development of antibiotic resistance.[11,15,16] Tetracyclines are considered first-line in oral antibacterial therapy, but if tetracyclines are contraindicated or not tolerated, macrolides may be used as second-line therapy.[3,11,14,16] Additionally, several statements recommend limiting the use of erythromycin due to increased resistance.[3,10] One guideline addressed the treatment of acne in children and recommends that in children under 8 years of age, for whom tetracyclines are contraindicated, macrolides and trimethoprim/sulfamethoxazole may be used with careful surveillance.[10]

Antibiotic Efficacy

Oral antibiotic efficacy in acne is likely to be multifactorial. Antibiotics may target *P. acnes* and the underlying inflammation contributing to acne development. Tetracyclines, macrolides, and clindamycin inhibit bacterial protein synthesis, while trimethoprim/sulfamethoxazole interferes with bacterial folate metabolism. Additionally, tetracyclines and, to a lesser extent, macrolides, inhibit neutrophil chemotaxis, cytokine production, and macro-phage function.[15,17]

The impact of antibiotics on *P. acnes* in the skin is controversial. In vitro testing has shown *P. acnes* are sensitive to tetracycline, doxycycline, minocycline, oxytetracycline, erythromycin, and penicillin, as well as to other antibacterials active against Gram-positive organisms.[18,19] However, in vivo, data are inconsistent. One study found a reduction in *P. acnes* after 3 weeks of tetracycline, minocycline, and clindamycin treatment, but not after treatment with penicillin or ampicillin.[20] Meanwhile, other in vivo studies have found no significant changes in skin bacterial flora in response to tetracycline or doxycycline treatment despite clinical improvement.[20–22]

Improvements in acne with systemic antibiotics may be seen without a simultaneous reduction in *P. acnes*. In fact, while the concentration of *P. acnes* correlates with sebum production, *P. acnes* concentration does not correlate with the amount of inflammation or acne severity. Instead, the inflammatory response in reaction to *P. acnes* has been correlated with acne severity.[16] Thus, it is believed that antibiotics that are both antibacterial and anti-inflammatory are most effective in the treatment of acne.

Various anti-inflammatory actions contribute to the efficacy of antibiotics in the treatment of acne. Tetracycline, erythromycin, and clindamycin inhibit neutrophil chemotaxis,[23,24] and tetracycline, doxycycline, and macrolides reduce the production of proinflammatory cytokines, such as interleukin-8 and tumor necrosis factor-α.[25,26] Tetracycline and erythromycin significantly inhibit the release of reactive oxygen species from human neutrophils.[27] These anti-inflammatory effects have been utilized in acne treatment, as well as in treating other inflammatory diseases such as periodontitis and rheumatoid arthritis.[28,29]

Efficacy of Individual Antibiotics. Only a few randomized controlled trials examined the efficacy of antibiotics in the treatment of acne compared with placebo. We identified nine randomized, placebo-controlled trials that investigated the efficacy of tetracycline,[30] doxycycline,[22,31] minocycline,[32,33] roxithromycin,[34] trimethoprim/sulfamethoxazole,[35,36] and clindamycin[37] (). Other antibiotics, such as lymecycline, erythromycin, and azithromycin have demonstrated efficacy in acne but have not been evaluated in randomized, placebo-controlled trials and are therefore not included in this review.

Table 2. Efficacy of oral antibiotics compared with placebo

Study (year)	Design	Type of acne	Treatment	Level of evidence[a]
Lane et al. (1969) [30]	Randomized, double-blind, placebo-controlled clinical trial. Age 12–29 years, *n* = 51	Diagnosis of acne vulgaris	Tetracycline vs. placebo	I
Plewig et al. (1970) [31]	Randomized, double-blind, placebo-controlled crossover trial. Age 14–27 years, *n* = 62	Inflammatory acne vulgaris	Doxycycline vs. placebo	I

Skidmore et al. (2003) [22]	Randomized, multicenter, double-blind, placebo-controlled trial. Age 18 years and older, *n* = 51	Moderate acne vulgaris	Doxycycline vs. placebo	I
Hersle and Gisslen (1976) [32]	Randomized, multicenter, double-blind, placebo-controlled crossover trial. Age 14–34 years, *n* = 43	Mild–moderate acne vulgaris	Minocycline vs. placebo	II
Fleischer et al. (2006) [33]	Randomized, multicenter, double-blind, placebo-controlled trial. Age 12–30 years, *n* = 451	Moderate–severe acne vulgaris	Minocycline vs. placebo	I
Ferahbas et al. (2004) [34]	Randomized, double-blind, placebo-controlled crossover trial. Age 14–30 years, *n* = 46	Inflammatory acne vulgaris	Roxithromycin vs. placebo	II
Hersle (1972) [35]	Randomized, double-blind, placebo-controlled crossover trial. Age 7–35 years, *n* = 43	Diagnosis of acne vulgaris	Trimethoprim/sulfamethoxazole vs. placebo	I
MacDonald et al. (1972) [36]	Randomized, double-blind, placebo-controlled crossover trial. Age 11–28 years, *n* = 33	Diagnosis of acne vulgaris	Trimethoprim/sulfamethoxazole vs. placebo	II
Christian and Krueger (1975) [37]	Randomized, double-blind, placebo-controlled trial. Age range not provided, *n* = 83	Moderate–severe acne vulgaris	Clindamycin vs. placebo	II

[a]Level of evidence: I = systematic review/meta-analysis of randomized controlled trials with consistent findings, high-quality individual randomized controlled trials, all-or-none studies; II = systematic review/meta-analysis of lower-quality clinical trials or studies with inconsistent findings, lower-quality clinical trial, cohort study, case-control study; III = consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence, or case series

Tetracycline: The efficacy of tetracycline was assessed in a randomized, double-blind, placebo-controlled trial in 51 patients with acne vulgaris.[30] Improvement was evaluated based on clinical and photographic assessment. After 6 weeks of tetracycline therapy, 54% of patients showed improvement compared with 7% of patients in the placebo group ($p < 0.01$). At the completion of the 3-month trial, clinical improvements were noted in 75% of the tetracycline group and only 33% of the placebo group ($p < 0.01$).

Doxycycline: A placebo-controlled, crossover trial was performed in 62 patients with inflammatory acne to evaluate the efficacy of doxycycline 100 mg daily compared with placebo.[31] Subjects were treated with doxycycline or placebo for 4 weeks during the first phase, followed by a 4-week rest period and a second 4-week phase in which the medications were switched. In each phase, patients treated with doxycycline had a significant reduction in inflammatory lesion count compared with the initiation of that phase (average lesion count decreased by 26% in the first phase [$p < 0.001$] and 24% in the second phase [$p < 0.05$]); however, patients treated with placebo had no significant reductions in inflammatory lesions in either phase of the study.[31] The study did not statistically compare the results of the doxycycline group with the placebo group. Another study investigating doxycycline 20 mg taken twice daily showed a reduction in the total number of lesions by 52%, compared with 18% with placebo after 6 months of treatment ($p < 0.01$).[22]

Minocycline: Despite the use of many different oral antibiotics for acne, extended-release minocycline administered at 1 mg/kg daily is the only US FDA-approved antibiotic specifically for moderate–severe inflammatory acne.[10] A crossover study evaluating the efficacy of minocycline showed a significant reduction of acne lesion score in the first phase of the minocycline group ($p < 0.05$), while the placebo-treated group acne score did not decrease significantly (no *p* value provided).[32] There was no comparison between the minocycline and placebo groups, and there was no washout period between the two phases of the crossover study to evaluate the results in the second phase of the trial.

Two 12-week, phase III studies examined safety and efficacy in 615 subjects treated with extended-release minocycline 1 mg/kg daily compared with 309 patients treated with placebo.[33] In both studies, patients treated with extended-release minocycline had a significant mean percentage reduction in inflammatory lesion count (43.1 and 45.8%) compared with placebo (31.7 and 30.8%) [$p < 0.001$ in both studies]. Furthermore, 16.6% of patients in the extended-release minocycline group had treatment success, graded by a dichotomized Evaluator's Global Severity Assessment scale, compared with 8.7% of patients in the placebo group (pooled analysis: $p < 0.001$).

Roxithromycin: Roxithromycin, a semi-synthetic macrolide, was evaluated in a crossover study.[34] Subjects were treated with roxithromycin 150 mg twice daily or placebo for 4 weeks and then underwent a 2-week washout period without any treatment, followed by the crossover of treatment for 4 weeks. Subjects treated with roxithromycin in the first phase of the study had significant reductions in median acne scores after 4 weeks compared with baseline ($p < 0.001$), whereas patients treated with placebo did not ($p > 0.05$). At the end of the second phase, and after both groups had been treated with a 4-week course of roxithromycin, all subjects had significantly decreased median acne scores compared with baseline ($p < 0.001$), and no difference was seen between groups ($p > 0.05$).[34]

Trimethoprim/Sulfamethoxazole: Trimethoprim/sulfamethoxazole is typically used when other antibiotics are contraindicated or not tolerated by the patient. Some consider it only as a third-line agent.[10,16] Two studies examined the efficacy of trimethoprim/sulfamethoxazole in randomized, double-blind, placebo-controlled, crossover trials.[35,36] Hersle[35] demonstrated a significant reduction in acne scores after 5 weeks of therapy with trimethoprim/sulfamethoxazole compared with baseline ($p < 0.001$) and with the placebo group ($p < 0.001$). In the second crossover trial, the authors did not present the raw data but reported no significant difference between treatment and placebo groups in the reduction in number of inflammatory and non-inflammatory lesions at the end of each phase ($p > 0.05$). However, when the authors analyzed inflammatory and non-inflammatory lesions separately, they concluded that there was a significant reduction in the number of inflammatory lesions compared with placebo, but there was no significant reduction in the number of non-inflammatory lesions compared with placebo.[36]

Clindamycin: When compared with placebo, oral clindamycin is effective in the treatment of acne.[37] In a double-blind, placebo-controlled trial, clinical improvement in acne was defined as at least 50% reduction in the number of papules and pustules compared with the number at initiation. After 13 weeks of therapy, 86% of clindamycin-treated patients and 38% of placebo-treated patients had clinical improvements ($p < 0.005$). The clindamycin and placebo groups had a 50 and 21% reduction in the number of comedones ($p < 0.05$) and a 78 and 26% reduction in inflammatory lesions ($p < 0.01$), respectively; however, the study did not report differences between the clindamycin and placebo groups. Additionally, participants were allowed to continue any therapies that they were already receiving at the start of the trial, including antibacterial soaps and cleansers.[16]

Comparison by Class of Oral Antibiotics. Despite the routine use of antibiotics for acne, there is little evidence that supports the use of one class of antibiotic over another. Additionally, there is considerable heterogeneity in the literature with regard to design and outcome measures in studies examining efficacy of various antibiotics,[38] making it difficult to establish evidence-based guidelines. Consequently, the choice of antibiotic is usually determined by the side-effect profile.

Different tetracycline antibiotics have been studied in the treatment of acne, but there is little evidence of superiority of one type over another (). A large, randomized, observer-blinded trial in patients with mild–moderate acne found comparable efficacy in reducing the number of inflammatory lesions compared with baseline between minocycline and oxytetracycline at 18 weeks.[39] Two studies examined the efficacy of lymecycline compared with minocycline.[40,41] Grosshans et al.[40] performed a randomized, multicenter, double-blind, double-dummy trial. At the end of 12 weeks, no difference was

noted between the lymecycline- and minocycline-treated groups in the percentage reduction of inflammatory lesion (50.6 and 52.2%, respectively) or total lesion count (44.5 and 42.9%, respectively). Bossuyt et al.[41] compared extended-release minocycline 100 mg daily with lymecycline 300 mg daily for 12 weeks. At the end of the trial, again, no significant difference was noted between the lymecycline and minocycline groups for mean percentage reductions in inflammatory lesion count (63 and 65%, respectively) and total lesion count (58 and 56%, respectively), or median percentage reduction in non-inflammatory lesion count (54 and 49%, respectively).[41]

Table 3. Efficacy of oral antibiotics compared with other antibiotic types or classes

Study (year)	Design	Type of acne	Treatment	Level of evidence[a]
Simonart et al. (2008) [38]	Systematic review	Mild–moderate inflammatory acne vulgaris	Oral tetracyclines in the treatment of acne	I
Ozolins et al. (2005) [39]	Randomized, observer-blinded, clinical trial. Age 12–39 years, *n* = 649	Mild–moderate acne vulgaris	Minocycline, oxytetracycline, benzoyl peroxide, and erythromycin/benzoyl peroxide	I
Garner et al. (2012) [42]	Systematic review	Inflammatory acne vulgaris	Randomized controlled trials comparing minocycline at any dose with other therapies	I
Grosshans et al. (1998) [40]	Randomized, multicenter, double-dummy controlled trial. Age 12–32 years, *n* = 144	Moderate–severe acne	Minocycline and lymecycline	I
Bossuyt et al. (2003) [41]	Randomized, investigator-blinded controlled trial. Age 12–30 years, *n* = 134	Acne severity grade between 1 and 5 (Leeds scale)	Minocycline and lymecycline	II
Babaeinejad et al. (2011) [43]	Randomized, double-blind clinical trial. Age range not provided, *n* = 100	Moderate acne vulgaris	Doxycycline and azithromycin	I
Kus et al. (2005) [44]	Randomized, investigator-blinded clinical trial. Age 18–30 years, *n* = 51	At least 10 inflammatory lesions, and no more than three nodules	Doxycycline and azithromycin	II
Maleszka et al. (2011) [45]	Randomized, double-blind, non-inferiority study. Age 14 years and older, *n* = 240	Moderate acne vulgaris	Doxycycline and azithromycin	II
Hayashi and Kawashima (2011) [46]	Randomized, multicenter, open-label controlled trial. Age 16 years and older, *n* = 150	Moderate–severe inflammatory acne vulgaris	Minocycline, roxithromycin, and faropenem	II
Gammon et al. (1986) [47]	Randomized, multicenter, double-blind clinical trial. Age 14–30 years, *n* = 200	Moderate–severe acne vulgaris	Tetracycline and erythromycin	I
Gibson et al. (1982) [48]	Randomized, single-blinded clinical trial. Age 14 years and older, *n* = 53	Inflammatory acne vulgaris	Oxytetracycline and trimethoprim	II

[a]For level of evidence categories, see Table 2

As a result, a systematic review of clinical trials on the efficacy of tetracycline, minocycline, doxycycline, and lymecycline for the treatment of mild–moderate inflammatory acne found no significant difference in reduction of inflammatory or non-inflammatory lesion count among various tetracyclines.[38] Furthermore, there is no evidence that second-generation tetracyclines, such as minocycline, are more effective than first-generation tetracyclines, despite superior pharmacokinetics and the higher cost of second-generation tetracyclines.[38,42] A Cochrane review concluded that the more expensive, extended-release minocycline formulation is neither more effective nor safer than other oral antibiotics.[42]

Studies have also compared different antibiotic classes in the treatment of acne. Three studies found similar efficacy of doxycycline and azithromycin.[43–45] Azithromycin is generally prescribed in pulsed doses, but with heterogeneity in scheduling and dosing of pulses. A randomized, double-blind study of patients with moderate acne confirmed the non-inferiority of pulsed azithromycin (500 mg daily for 3 days in week 1, then 500 mg weekly for 9 weeks) compared with daily doxycycline, and reported no difference in the incidence of adverse events.[45] Studies that compared daily doxycycline with pulsed azithromycin, by Kus et al.[44] (500 mg/day for 3 days/week in month 1, then 2 days/week in month 2, and then 1 day/week in month 3) and Babaeinejad et al.[43] (500 mg daily for 4 consecutive days per month for 3 months), also showed comparable efficacy between the two antibiotics for moderate inflammatory acne. However, Babaeinejad et al. reported a significantly greater improvement in patients older than 18 years of age receiving daily doxycycline compared with pulsed azithromycin.[43]

A randomized, multicenter, open-label, controlled trial compared minocycline 100 mg daily with roxithromycin 150 mg daily and faropenem 200 mg three times daily in patients with moderate to severe inflammatory acne. A significant decrease in lesion count was noted, compared with baseline, in all three treatment groups, but no significant difference between groups at week 4 or 4 weeks post-treatment. Additionally, there was no significant difference in adverse events between groups.[46] However, the inability to detect significant differences between antibiotic classes is not surprising given the small sample size (*n* = 150) and short treatment duration.[42]

Oral erythromycin has been effective in the treatment of acne. A randomized, double-blind, clinical trial that studied the efficacy of erythromycin and tetracycline showed that, at week 12, erythromycin significantly reduced inflammatory lesion count by 67% and non-inflammatory lesion count by 22%, and tetracycline significantly reduced inflammatory lesion count by 64% and non-inflammatory lesion count by 34%. No differences in efficacy were seen between the erythromycin and tetracycline groups.[47] Despite the equivalent efficacies, erythromycin is not recommended for acne due to increased microbial resistance.[15]

Finally, trimethoprim has been studied in the treatment of acne. In a small, randomized, single-blinded trial, the use of trimethoprim 100 mg (three times per day for 4 weeks, then twice daily for 4 weeks) was as effective in reducing lesion count as oxytetracycline 250 mg (three times per day for 4 weeks, then twice daily for 4 weeks). However, two patients in the trimethoprim treatment group were withdrawn from the trial secondary to suspected drug-related eruptions.[48]

Efficacy at Different Antibiotic Doses. There are many randomized, controlled, dose-ranging studies for oral tetracyclines in the treatment of acne, but hardly any in other antibiotic classes (). A systematic review of tetracycline use in acne found that mean drug dosage varied from 375–1000 mg daily for first-generation tetracyclines, between 40 and 200 mg daily for doxycycline, between 50 and 100 mg daily for minocycline, and between 150 and 300 mg daily for lymecycline.[38] Oral tetracycline is usually prescribed at 500 mg twice daily, but food and dairy products reduce its absorption. Doxycycline is traditionally prescribed at 50–100 mg twice daily, and may be taken with food. Finally, minocycline is usually prescribed in a range of 50–100 mg once or twice daily, and lymecycline at 300 mg daily.[10,15,49] The recommended dosages for erythromycin are 250–500 mg daily or twice daily, and 160–800 mg twice daily for trimethoprim/sulfamethoxazole.[10,15] Azithromycin has largely been evaluated in open-label studies that utilize various pulse dosing regimens ranging from 3 times per week to 4 days per month.[3]

Table 4. Dose comparisons

Study (year)	Design	Type of acne	Treatment	Level of evidence[a]
Leyden et al. (2013) [50]	Randomized, phase II, double-blind study. Age 12–45 years, *n* = 257	Moderate–severe inflammatory acne	Doxycycline	I
Moore et al. (2015) [51]	Randomized, multicenter, phase II, double-blind, controlled trial. Age 12 years and older, *n* = 662	Moderate–severe acne	Doxycycline	I
Toossi et al. (2008) [52]	Randomized, double-blind controlled trial. Age 18 years and older, *n* = 100	Moderate acne	Doxycycline	II
Pierard-Franchimont et al. (2002) [57]	Randomized, double-blind clinical trial. Age 17–35 years, *n* = 86	Moderate–severe acne	Minocycline	I
Stewart et al. (2006) [58]	Randomized, multicenter, double-blind, placebo-controlled trial. Age 12–30 years, *n* = 233	Moderate–severe acne	Minocycline	I
Dubertret et al. (2003) [59]	Randomized, multicenter, double-blind, controlled trial. Age 16–40 years, *n* = 271	Moderate–severe acne	Lymecycline	I
Basta-Juzbasic et al. (2007) [60]	Randomized, multicenter, open-label, controlled trial. Age 16 years and older, *n* = 120	Papulopustular acne	Azithromycin	II

[a]For level of evidence categories, see Table 2

In the first published dose-ranging study for doxycycline, patients with moderate to severe inflammatory acne were randomized to receive placebo or doxycycline 0.6, 1.2, or 2.4 mg/kg/day for 12 weeks.[50] Subjects treated with doxycycline 2.4 mg/kg had a greater mean percentage decrease in inflammatory lesions compared with placebo at 12 weeks (49.0 and 27.0%, respectively). There was a 29.4 and 40% mean reduction in inflammatory lesion count in the doxycycline 0.6 or 1.2 mg/kg/day groups, respectively, which was not significantly different compared with placebo. However, the authors note that the study was not prospectively powered to detect efficacy differences among groups, therefore future studies would need to confirm the dose response of doxycycline in the treatment of acne.[50]

In order to curb the rise of antibiotic resistance, low, subantimicrobial dose doxycycline has been studied in the treatment of acne.[22,51,52] Doxycycline 20 mg twice daily produces maximum mean and steady-state plasma levels of doxycycline significantly lower than the minimum inhibitory concentration required to produce antimicrobial effects.[53] Doses of doxycycline <50 mg/day are considered subantimicrobial.[17] Studies in periodontal disease have shown no antimicrobial effects on total bacterial counts, normal flora, periodontal opportunistic pathogens, or antibiotic susceptibility of subgingival flora after long-term treatment with subantimicrobial doxycycline 20 mg twice daily, relative to placebo.[54,55] Additionally, no effect on the dominant bacterial flora in samples taken from the mouth, skin, intestinal tract, or vagina was seen in in vivo studies of subantimicrobial dose doxycycline taken for 6–18 months.[56]

Submicrobial doses of doxycycline have been shown to be effective in the treatment of acne. Two trials examined the efficacy of subantimicrobial dose doxycycline at 20 mg twice daily for moderate acne.[22,52] Skidmore et al.[22] performed a randomized, double-blind, placebo-controlled trial and demonstrated that subantimicrobial-administered oxycycline, compared with placebo, significantly reduced the number of inflammatory lesions (50.1 and 30.2%, respectively; $p = 0.04$), number of comedones (53.6 and 10.6%, respectively; $p < 0.01$), and total number of lesions (52.3 and 17.5%, respectively; $p < 0.01$) at 12 weeks. Subantimicrobial dose doxycycline also had no effect on the number or severity of resistant organisms when compared with placebo.[22] In the second trial, subantimicrobial dose doxycycline was effective and displayed a superior safety profile when compared with doxycycline 100 mg daily,[52] but the authors did not report on the impact of skin flora.

Moore et al.[51] performed a dose-ranging study of doxycycline, comparing the safety and efficacy of submicrobial modified-release doxycycline 40 mg daily with doxycycline 100 mg daily and placebo in patients with moderate–severe acne. Doxycycline 100 mg daily had a significantly higher 'success rate', defined as the percentage of subjects who were scored 'clear' or 'almost clear' after 16 weeks of therapy, compared with placebo (13.8 vs. 7.7%, respectively; $p = 0.035$). However, doxycycline 100 mg was not more effective than placebo in mean change in inflammatory lesion count (12.9 vs. 12.6, respectively; $p = 0.595$), median percentage reduction in inflammatory lesion count (47.3 vs. 44.3%, respectively; $p = 0.703$), or percentage change in total lesion count (35.9 vs. 34.1%, receptively; $p = 0.972$). In contrast, modified-release doxycycline 40 mg daily was significantly more effective than placebo in mean reduction in inflammatory lesion count (16.1 vs. 12.6, respectively; $p = 0.006$), median percentage reduction in inflammatory lesion count (51.6 vs. 44.3%, respectively; $p = 0.003$), or median percentage reduction in total lesion count (41.7 vs. 34.1%, respectively; $p = 0.004$). However, modified-release doxycycline 40 mg was not significantly more effective than placebo in mean reduction of non-inflammatory lesion count at 16 weeks (10.0 vs. 5.8, respectively; $p = 0.445$) and did not demonstrate a significantly greater success rate compared with doxycycline 100 mg (14.4 vs. 13.8%, respectively; $p = 0.877$). The incidence of drug-related adverse events for modified-release doxycycline was similar to placebo (3.7 vs. 4.1%, respectively) and relatively lower than doxycycline 100 mg (3.7 vs. 17%). The authors concluded that modified-release doxycycline 40 mg was comparable in efficacy and superior in safety to doxycycline 100 mg.[51]

Although minocycline is typically prescribed in a range of 50–100 mg daily to treat acne, which is half the dose for other indications, no studies have compared the efficacy of this dosing to the efficacy of standard 100–200 mg daily dosing for the treatment of acne.[42] A small, randomized controlled trial compared minocycline 50 mg daily for 12 weeks with 50 mg twice daily for 4 weeks, followed by 50 mg daily for 8 weeks.[57] A significantly greater reduction in the number of inflammatory papules in the 50 mg twice daily/50 mg daily group was found compared with the 50 mg daily group; however, the study was limited by its small size and a lack of control for confounders.[42]

A phase two, multicenter, randomized controlled trial compared doses of extended-release minocycline and placebo.[58] Subjects in the treatment group, stratified based on the their weight, were randomized to 1, 2, or 3 mg/kg daily extended-release minocycline. At 12 weeks, the number of inflammatory lesions had decreased by 46.6% in the 3 mg/kg group, 49.3% in the 2 mg/kg group, 56.8% in the 1 mg/kg group, and 39.4% in the placebo group compared with baseline. The only significant difference when compared with placebo was seen in the 1 mg/kg group ($p = 0.015$). No dose-dependent

effect was observed in global assessment scores or reduction in the number of total lesions compared with baseline; however, it was likely the study did not have enough participants to detect a dose-dependent effect.[42]

Lymecycline is a second-generation tetracycline and is routinely prescribed in Europe. In an effort to increase medication adherence, Dubertret et al.[59] performed a randomized, double-blind, placebo-controlled trial to explore the efficacy of once-daily dosing of lymecycline 300 mg compared with lymecycline 150 mg twice daily and compared with placebo. Lymecycline 300 mg daily significantly reduced the number of inflammatory lesions (62.0 vs. 35.6%; $p = 0.0005$) and number of total lesions compared with placebo ($p < 0.0007$) at 12 weeks. Among the lymecycline 300 mg and lymecycline 150 mg twice-daily groups, the percentage reduction in inflammatory counts (62 and 54%, respectively) and total lesion counts (52 and 47%, respectively) were similar throughout the 12-week study. Furthermore, no significant difference in global improvement score was noted between the two groups at the end of 12 weeks. Similar rates of drug-related side effects were observed in all three groups.[59]

Doses of antibiotics for acne outside of the tetracycline class are less well-studied. One randomized, multicenter, dose-ranging trial investigated the optimal dose regimen of azithromycin in 120 patients with papulopustular acne vulgaris.[60] Each subject was randomized to one of three treatment groups: azithromycin total dose 4.5 g in 7 weeks, total dose 6.0 g in 10 weeks, or total dose 7.5 g in 13 weeks. Azithromycin 4.5 g was less effective than the other treatments in decreasing the sum of lesions and change over time ($p = 0.03$ and 0.02, respectively). No significant differences in the occurrence of adverse events were noted among the three groups. The authors recommended 6.0 g in 10-week dosing because of its comparable efficacy with the higher-dose group, but lower cost.[60]

Efficacy of Different Antibiotic Durations. Most of the studies identified examined the efficacy of antibiotics for 12 weeks, but studies ranged in duration from 4 to 24 weeks. In their systematic review of clinical trials investigating the efficacy of oxytetracycline, lymecycline, doxycycline, and minocycline for inflammatory acne, Simonart et al.[38] found that duration of assessment varied between 8 and 24 weeks for first-generation tetracyclines, and between 4 and 24 weeks for second-generation tetracyclines. Ozolins et al.[39] showed that improvements from oral antibiotics, specifically minocycline and oxytetracycline, mainly occur in the first 6 weeks; however, variation in the duration of trials and different clinical assessment time points make it difficult to determine the optimal duration of antibiotic use to guide evidence-based practice.

According to consensus guidelines, antibiotics should be used for a minimum of 6–8 weeks,[9,11,15] with the expectation of an initial clinical response in 4–8 weeks.[9,15] Ideally, antibiotics should be used for no more than 12 weeks,[3] but recommendations differ if a patient has little or no clinical improvement after 12 weeks of therapy. One study recommends discontinuing antibiotics if no improvement is seen by 12 weeks,[9] whereas other studies allow longer durations of up to 6 months with consistent follow up and re-evaluation.[3,16] Ultimately, the goal is to limit antibiotic duration to the least amount of time required for a clinical response, and to maintain the improvement with topical therapies.

Adherence with the consensus guidelines for antibiotic duration has been examined in three retrospective studies.[61–63] In adolescents, Lee et al.,[61] using a claims database, found that the overall mean duration for antibiotic use was 129 days; 17.53% of the courses were over 180 days (6 months).[61] In adults, Straight et al.[62] found similar results, with a mean antibiotic duration of 125 and 15.5% of the courses lasting longer than 6 months. In a third chart review, patients with severe inflammatory acne who were eventually treated with isotretinoin had a mean antibiotic duration of 331.3 days, and 64.2 and 33.6% of patients had antibiotic courses of 6 months or longer and 1 year or longer, respectively.[63] These studies show many patients are taking antibiotics for longer than the recommended durations, and demonstrate a practice gap between consensus guidelines and clinical practice.

Comparison With Topical Antibiotic Therapy. In an effort to decrease the use of long-term systemic antibiotics, dermatologists have used topical antibiotics, including tetracycline, erythromycin, and clindamycin. Topical antibiotics, like systemic antibiotics, are presumed to have both antibacterial and anti-inflammatory effects.[3]

We identified six trials that compared oral tetracycline with topical therapy (),[64–69] two of which were randomized, double-blind, placebo-controlled trials comparing the efficacy of oral tetracycline with topical tetracycline therapy.[64,65] Blaney and Cook[64] found significant reductions in acne severity in the oral tetracycline group and the topical tetracycline by week 13 compared with placebo, but no significant differences were noted between the oral and topical tetracycline groups. In a second study, the oral tetracycline group had significant reductions in mean acne severity grade starting at week 4, while the topical tetracycline group showed significant reductions in mean acne severity starting at week 7; however, no significant difference in mean acne severity was noted between the oral and topical tetracycline groups at any time points.[65] In both studies, subjects treated with topical tetracycline experienced stinging/burning with application, and mild yellowish discoloration.[64,65]

Table 5. Topical comparisons

Study (year)	Design	Type of acne	Treatment	Level of evidence[a]
Blaney and Cook (1976) [64]	Randomized, double-blind, placebo-controlled trial. Age 11–25 years, *n* = 75	Moderate–severe acne	Tetracycline and topical tetracycline	II
Smith et al. (1976) [65]	Randomized, double-blind, controlled trial. Age 18–25 years, *n* = 135	Cook acne grade 2 and higher	Tetracycline and topical tetracycline	II
Gratton et al. (1982) [67]	Randomized, multicenter, double-blind, controlled trial. Age 18–35 years, *n* = 305	Moderate–severe acne	Tetracycline and topical clindamycin	II
Braathen (1984) [66]	Randomized, double-blind, controlled trial. Age 16–25 years, *n* = 87	Moderate–severe acne	Tetracycline and topical clindamycin	II
Katsambas et al. (1987) [69]	Randomized, double-blind, controlled trial. Age 12–30 years, *n* = 44	Moderate acne	Tetracycline and topical clindamycin	II
Sheehan-Dare et al. (1990) [70]	Randomized, matched-pair, double-blind, controlled trial. Age 14–35 years, *n* = 66	Moderate–severe acne	Minocycline and topical clindamycin	II
Rapaport et al. (1982) [68]	Randomized, double-blind, controlled trial. Age 12–40 years, *n* = 54	Moderate acne	Tetracycline and topical erythromycin	I
Norris et al. (1991) [71]	Randomized, double-blind, controlled trial. Age 12–33 years, *n* = 69	Mild–moderate acne	Oxytetracycline, topical tetracycline, benzoyl peroxide	I

[a]For level of evidence categories, see Table 2

Three studies identified compared oral tetracycline with clindamycin 1% topical solution.[66,67,69] Two of the studies were 8-week, randomized, double-blind, placebo-controlled trials in patients with moderate–severe acne.[66,67] Gratton et al.[67] demonstrated that both oral tetracycline and topical clindamycin significantly reduced the mean number of papules compared with placebo ($p < 0.05$ for both comparisons) by 8 weeks. However, compared

with placebo, the topical clindamycin group significantly reduced the number of pustules by week 4 (28 ± 40 vs. 15 ± 26, respectively; $p < 0.05$), whereas, compared with placebo, the tetracycline group only had a significant reduction in pustules by week 8 (27 ± 45 vs. 15 ± 23, respectively; $p < 0.05$). Braathen[66] showed similar results; both topical clindamycin and oral tetracycline significantly reduced papule count, pustule count, and inflammatory lesion count starting at weeks 4, 2, and 2, respectively; however, the topical clindamycin group had a greater reduction in pustule count at week 2 and papule count at week 4 compared with tetracycline ($p = 0.0004$). Furthermore, at 8 weeks, the topical clindamycin group had a 72% reduction in mean inflammatory lesion count compared with a 57% reduction in the oral tetracycline group ($p = 0.0004$).[66] There were no dropouts due to side effects in either study, and the authors concluded that topical clindamycin is as effective, and perhaps superior, to oral tetracycline. Unlike the previous studies, a longer, 12-week trial observed no significant differences in the reduction of papules, pustules, or open and closed comedones compared with baseline between oral tetracycline and topical clindamycin.[69] In addition to topical tetracycline and topical clindamycin, the efficacy of oral tetracycline has been compared with topical erythromycin. In a double-blind study, Rapaport et al.[68] concluded that topical erythromycin displayed an effect earlier and had fewer side effects than oral tetracycline.[68]

Minocycline 50 mg twice daily has been compared with clindamycin 1% topical solution. In a 12-week, double-blind trial, both minocycline and clindamycin significantly decreased inflammatory, but not non-inflammatory, lesion counts compared with baseline.[70] Although no significant difference was noted between the two treatments, there was a noted trend of superiority in the topical clin-damycin group.[42] A large, 18-week trial compared extended-release minocycline, oxytetracycline, 5% ben-zoyl peroxide, and two different combination regimens of benzoyl peroxide and topical erythromycin.[39] The two different topical combination therapies were the most effective in reducing the number of inflammatory lesions, but the difference was not significant. As expected, there were more systemic side effects with oral antibiotics and more local irritation with topical therapy.

A final study compared oxytetracycline with topical tetracycline and 5% benzoyl peroxide gel in 69 patients with mild–moderate acne.[71] While all three treatment groups significantly reduced the number of non-inflammatory lesions at the end of 12 weeks (oxytetracyline 25% reduction, $p = 0.024$; topical tetracycline 46% reduction, $p < 0.003$; 5% benzoyl peroxide 58% reduction, $p < 0.001$), only the topical tetracycline and 5% benzoyl peroxide groups significantly reduced the number of inflammatory lesions at 12 weeks (topical tetracycline 35% reduction, $p = 0.019$; 5% benzoyl peroxide 42% reduction, $p < 0.001$). No significant differences were noted between the groups in either the reduction in the number of non-inflammatory or inflammatory lesions or acne severity grade.[71]

Combination Therapy. Current evidence-based guidelines for the treatment of acne recommend combining oral antibiotics with topical retinoids and/or benzoyl peroxide. Retinoids bind nuclear retinoic acid receptors to normalize follicular keratinocyte differentiation and are effective against comedonal and inflammatory acne.[6] Benzoyl peroxide is an antibacterial agent with some comedolytic activity.

Several studies have examined oral therapy in combination with topical retinoids (). A large, randomized, multicenter clinical trial demonstrated that combination therapy of doxycycline with adapalene 0.1% gel compared with doxycycline alone had a significantly greater reduction in percentage change from baseline in the number of inflammatory (64.6 vs. 58.5%, respectively; $p = 0.02$), non-inflammatory (60.3 vs. 40.5%, respectively; $p < 0.001$) and total (61.2 vs. 45.3%, respectively; $p < 0.002$) lesions in patients with severe facial acne vulgaris at 12 weeks.[72] Additionally, this significant difference was apparent as early as week 4, signifying that oral antibiotic and topical combination therapy is both more effective and faster than antibiotic treatment alone.[72] Studies comparing oral faropenem/adapalene combination therapy and oral lymecycline/adapalene combination therapy also demonstrated the increased efficacy of an oral antibiotic/topical retinoid combination therapy.[73,74]

Table 6. Combination comparisons

Study (year)	Design	Type of acne	Treatment	Level of evidence[a]
Thiboutot et al. (2005) [72]	Randomized, multicenter, investigator-blinded clinical trial. Age range not provided, *n* = 467	Severe facial acne vulgaris	Doxycycline and adapalene gel	I
Hayashi and Kawashima (2012) [73]	Randomized, multicenter, open-label, controlled trial. Age 16 years and older, *n* = 149	Moderate–severe acne	Faropenem and adapalene gel	II
Cunliffe et al. (2003) [74]	Randomized, multicenter, investigator blinded, clinical trial. Age 12–30 years, *n* = 217	Moderate–severe inflammatory acne	Lymecycline and adapalene gel	I
Tan et al. (2012) [75]	Randomized, multicenter, double-blind controlled trial. Age 12–35 years, *n* = 243	Severe facial acne vulgaris	Doxycycline and adapalene gel/benzoyl peroxide	I
Gold et al. (2010) [76]	Randomized, multicenter, double-blind study. Age 12–35 years, *n* = 459	Severe facial acne vulgaris	Doxycycline and adapalene gel/benzoyl peroxide	I
Dreno et al. (2011) [77]	Randomized, double-blind controlled trial. Age 12–35 years, *n* = 378	Moderate–severe acne	Lymecycline and adapalene gel/benzoyl peroxide	I

[a]For level of evidence categories, see Table 2

Combination treatments with retinoids and benzoyl peroxide have also been studied with systemic antibiotics. Two studies compared the efficacy of doxycycline 100 mg daily in combination with adapalene 0.1%/benzoyl peroxide 2.5% and doxycycline with a topical vehicle in patients with severe facial acne. Both studies demonstrated a significant reduction in inflammatory, non-inflammatory, and total lesion count in patients treated with combination oral and topical therapy.[75,76] Finally, adapalene 0.1% gel/benzoyl peroxide 2.5% in combination with lymecycline 300 mg daily compared with a lymecycline 300 mg daily/topical placebo group showed a significantly greater median percentage change from baseline in the number of inflammatory (81.7 vs. 71.0%, respectively; $p < 0.001$) and non-inflammatory (71.7 vs. 52.5%, respectively; $p < 0.001$) lesions.[77] A significant difference in total lesion count between the groups became apparent as early as week 2 (25.6 vs. 18.2%, $p < 0.001$). Finally, patients in the combination group were significantly more satisfied at the end of treatment.[77]

Topical therapy has also been shown to prolong remission rates after systemic antibiotic therapy for acne. Tan et al.[75] demonstrated that after 12 weeks of oral and topical combination therapy, 24 weeks of adapalene 0.1%/benzoyl peroxide 2.5% maintenance therapy prevents relapse and promotes progressive efficacy of the induction therapy compared with patients treated with 12 weeks of combination therapy followed by a topical placebo.

Side Effects. The choice of antibiotic, especially within the tetracycline family, may depend on the side effects of each drug. The most frequently reported side effects of antibiotics used in the treatment of acne are listed in .

Table 7. Side effects of oral antibiotics commonly used in the treatment of acne vulgaris

Side effect	Tetracycline	Doxycycline	Minocycline	Lymecycline	Azithromycin	Erythromycin	Trimethoprim/sulfamethoxazole	Cl

Photosensitivity	X	X[a]	X	X			X	
GI disturbance	X (nausea, vomiting, diarrhea)	X (nausea, vomiting, diarrhea, pill esophagitis)[a]	X (nausea, vomiting, diarrhea)	X (nausea, vomiting, diarrhea)	X (nausea, vomiting, diarrhea)	X (nausea, vomiting, diarrhea)	X (nausea, vomiting, diarrhea)	X (nau diarrh pseud colitis
Vaginal candidiasis	X	X	X					
Vestibular side effects			X (tinnitus, dizziness)					
Pigment deposition			X[b]					
Cardiac conduction Abnormality					X	X		
AI disorders			X (lupus-like syndrome, arthritis, thyroiditis, polyarteritis nodosa, hepatitis)					
Drug eruptions			X (SJS, DRESS)		X (cutaneous hypersensitivity reaction)		X (SJS, TEN)	X (DR
Pseudotumor cerebri	X	X	X	X				
Hematopoietic system disorder							X (neutropenia, agranulocytosis, aplastic anemia, thrombocytopenia)	
Hepatotoxicity			X (hepatitis, hypersensitivity, or autoimmune)				X (fulminant hepatitis necrosis)	

AI autoimmune, *DRESS* drug reaction with eosinophilia and systemic symptoms, *GI* gastrointestinal, *SJS* Stevens–Johnson Syndrome, *TEN* toxic epidermal necrolysis
[a]Dose-dependent
[b]Dose-dependent and length of treatment-dependent

Resistance/Microbiome

Antibiotic resistance is a worldwide concern. According to the Centers for Disease Control and Prevention in 2013, drug-resistant bacteria account for 23,000 deaths annually in the US.[78] The routine long-term use of antibiotics in the treatment of acne has resulted in antibiotic resistant *P. acnes* and changes in the steady state microbiome. Antibiotic resistance in *P. acnes* was first recognized in 1979[16] and is now reported all over the world, with at least 50% of acne patients colonized with erythromycin- and clindamycin-resistant *P. acnes*.[79]*P. acnes* resistance mainly arises from chromosomal point mutations, but *P. acnes* does not generally acquire resistance from, or transfer resistant determinants to, other bacteria.[80] However, patients can be colonized with antibiotic-resistant strains of *P. acnes* without ever having taken an antibiotic because of transmission from close contacts treated with antibiotics.[79]

Although improvements in acne do not always correlate with reductions in *P. acnes*,[22]*P. acnes* resistance to antibiotics still appears to be clinically relevant and may manifest as a reduced response, no response, or relapse.[9] Antibiotic-resistant *P. acnes* is correlated with longer duration of acne and longer duration of antibiotic treatment.[80] As acne lesions behave as independent follicular infections made up of unique mixtures of susceptible and/or resistant strains of *P. acnes*, the greater number of follicles with antibiotic-resistant *P. acnes* may result in a diminished response to treatment.[28] This diminished response in patients colonized with antibiotic-resistant *P. acnes* has been shown in patients treated with oral erythromycin, tetracycline, minocycline, and oxytetracycline.[39,81,82] Furthermore, *P. acnes* has also been implicated in other infections such as endocarditis, mediastinitis, prosthetic joint infections, and septic arthritis,[9,80] making *P. acnes* resistance a concern in diseases, except acne.

The overuse of oral antibiotics for the treatment of acne also has consequences for non-target bacteria. In a cross-sectional study of 105 patients, Levy et al.[83] found a threefold increase in the prevalence of Streptococccus pyogenes colonization in the oropharynx of patients undergoing topical and/or oral antibiotic therapy for acne compared with those not using any antibiotics ($p = 0.003$). Those who used oral or topical antibiotics had similar increases in prevalence of *S. pyogenes* colonization compared with patients not taking any antibiotics. Long-term antibiotic therapy has also been associated with multidrug-resistant gastrointestinal tract flora,[84] coagulase-negative staphylococci, and *Staphylococcus aureus*.[85]

Pharyngitis is another clinical consequence of long-term antibiotic use for acne. A retrospective cohort study showed that patients receiving oral and/or topical antibiotic therapies had approximately two times greater odds of an upper respiratory tract infection diagnosed by a general practitioner compared with acne patients not receiving antibiotic treatment (odds ratio [OR] 2.15, 95% confidence interval [CI] 2.05–2.23; $p < 0.001$).[86] A cross-sectional study followed by a 9-month prospective cohort study in college students confirmed this association.[87] The cross-sectional portion found a 3.5-fold increase in the odds of self-reporting an episode of pharyngitis in students with acne taking oral antibiotics compared with those with acne not taking antibiotic therapy. In the longitudinal portion of the study, the OR associating oral antibiotic use with pharyngitis was 4.34 (95% CI 1.51–12.47), and an estimated relative risk of 3.91.[87] Despite this trend, there was no association between colonization with group A streptococcus or *Streptococcus salivarius*, an inhibitor of group A streptococcus growth that is sensitive to tetracycline antibiotics, with either episodes of pharyngitis or antibiotic use. Thus, the association between the use of oral antibiotics for acne and pharyngitis has been established, but the mechanism of this association has not been elucidated.[87]

In a retrospective cohort study using a medical database of 94,487 individuals with acne in the UK, individuals exposed to tetracyclines, particularly doxycycline, had an increased risk for developing inflammatory bowel disease compared with those who did not receive antimicrobials (hazard ratio 1.39 for the tetracycline class, 1.63 for doxycycline).[88] Although a causal association between antibiotics and inflammatory bowel disease has not been established, the effect of antibiotic on gut flora, gut cellular activity, and T-cell activity may be associated with new-onset inflammatory bowel disease.[88] These studies demonstrate the concern that prolonged use of oral antibiotic therapy for acne not only impacts *P. acnes* resistance but also has implications for antibiotic resistance in commensal flora at other body sites, and for the development of different diseases.

Discussion

The intent of this review was to critically evaluate the literature on the use of oral antibiotics in the treatment of acne. Oral antibiotics are effective in the treatment of inflammatory acne compared with placebo, but only extended-release minocycline is actually FDA-approved for the treatment of acne. There is no evidence to support the superior efficacy of one type or class of antibiotic over another, but tetracyclines are generally regarded as first-line therapy and macrolides as second-line therapy due to increasing antimicrobial resistance to macrolides. Trimethoprim/sulfamethoxazole is also effective in treating acne, but patients should be monitored closely while taking this antibiotic because of possible severe side effects. The ideal dose and duration of antibiotic therapy could not be determined since different antibiotics and treatment regimens were evaluated. However, the duration of antibiotic use should be limited to 3 months, when possible, and results should be maintained with a topical retinoid and/or benzoyl peroxide to prevent relapse and curb the rise in antibiotic resistance.

Future studies should continue to evaluate the long-term impact of oral antibiotics used for acne and associations with diseases resulting from alterations in the steady-state microbiome. Furthermore, additional research should investigate whether resident commensal bacteria remain unaffected by long-term submicrobial dose therapy. There are also limited data on the follicular concentration of antibiotics generally and at specific doses. Finally, more therapies should be studied in the treatment of moderate inflammatory acne to eventually shift the mainstay of acne therapy away from oral antibiotics and towards other treatment modalities.

Conclusions

We aimed to comprehensively review the published data on oral antibacterial therapy in acne. Based on this review, tetracyclines, macrolides, and trimethoprim/sulfamethoxazole are all safe and effective in the treatment of moderate–severe inflammatory acne. Oral antibiotics should be prescribed with concurrent topical therapy for better results and to combat antibiotic resistance. The heterogeneity of acne trials makes it challenging to determine the most superior type, dose, or duration of antibiotics. Consequently, the choice of antibiotic should be determined based on the side-effect profile, bacterial resistance, cost, and consensus guidelines. Dermatologists should continue to investigate the long-term effects of antibacterial therapy on target and non-target bacteria, and study newer treatments for patients with inflammatory acne.

Sidebar

Key Points

The use of oral antibiotics is reserved for patients with moderate to severe inflammatory acne.

Tetracyclines are considered first-line therapy, while macrolides and trimethoprim/sulfamethoxazole are acceptable alternative agents.

It is recommended that oral antibiotics be prescribed with concurrent topical therapy for improved efficacy and to combat antibiotic resistance.

Oral antibiotics used in the treatment of acne may have unintended effects on non-target bacteria, and the clinical implications of this warrant further exploration.

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