Received: 2 November 2020 | Accepted: 30 November 2020

DOI: 10.1002/der2.49

INVITED REVIEW

Dermatological Reviews WILEY

Treating acne with the tetracycline class of antibiotics: A review

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Abstract

Acne, one of the most common dermatologic conditions seen by dermatologists, is frequently treated with oral antibiotics. As such, dermatologists prescribe more antibiotics than any other specialty, the majority of which are of the tetracycline class. This family of antibiotics includes tetracycline, doxycycline, minocycline, and sarecycline. Although linked by a similar mechanism of action, each agent has unique characteristics that should be considered carefully. Sarecycline, recently approved by the United States Food and Drug Administration, is a narrow-spectrum antibiotic and acts primarily on cutaneous bacteria such as *Cutibacterium acnes*. In contrast, tetracycline, doxycycline, and minocycline are broad-spectrum antibiotics—indiscriminately inhibiting bacteria in both the skin and gastrointestinal tract. Rising concerns about antibiotic resistance and the need for antibiotic stewardship may make a narrow-spectrum antibiotic a more attractive therapeutic choice for the acne patient. It is vital that the clinician understand the pros and cons of each tetracycline agent so as to optimally serve our acne population.

KEYWORDS
acne, antibiotic, doxycycline, minocycline, sarecycline, tetracycline

1 | BACKGROUND

Dermatologists prescribe more antibiotics per patient than any other specialty.[1] Per provider, dermatologists prescribed 572 oral antibiotics annually compared to 293 for providers of other specialties in 2017.[2] This fact is not surprising given the prevalence of acne patients and their need for oral antibiotics. Approximately 50 million people in the United States suffer from acne vulgaris and acne is one of the top three diagnoses among all age groups in dermatology clinics.[3] *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*), part of the normal skin flora, plays a key role in acne pathogenesis. The tetracycline class of antibiotics inhibits *C. acnes* growth in the pilosebaceous unit thus making the tetracyclines successful in treating acne.[4]

2 | TETRACYCLINES FAMILY—OVERVIEW

The tetracyclines (Figure 1) are the most widely studied and frequently prescribed oral antibiotics for acne and the only class of antibiotics with the United States Food and Drug Administration (FDA) indications for acne treatment. Shortly after the isolation of the parent compound, chlortetracycline, from *Streptomyces aureofaciens* in 1947, reports of the success of the tetracycline family of compounds in treating acne were published.[5,6] Since its discovery, the tetracycline family has broadened to include synthetic compounds or modifications of naturally occurring tetracyclines. The most commonly prescribed semi-synthetic tetracyclines include the second-generation members doxycycline and minocycline, which

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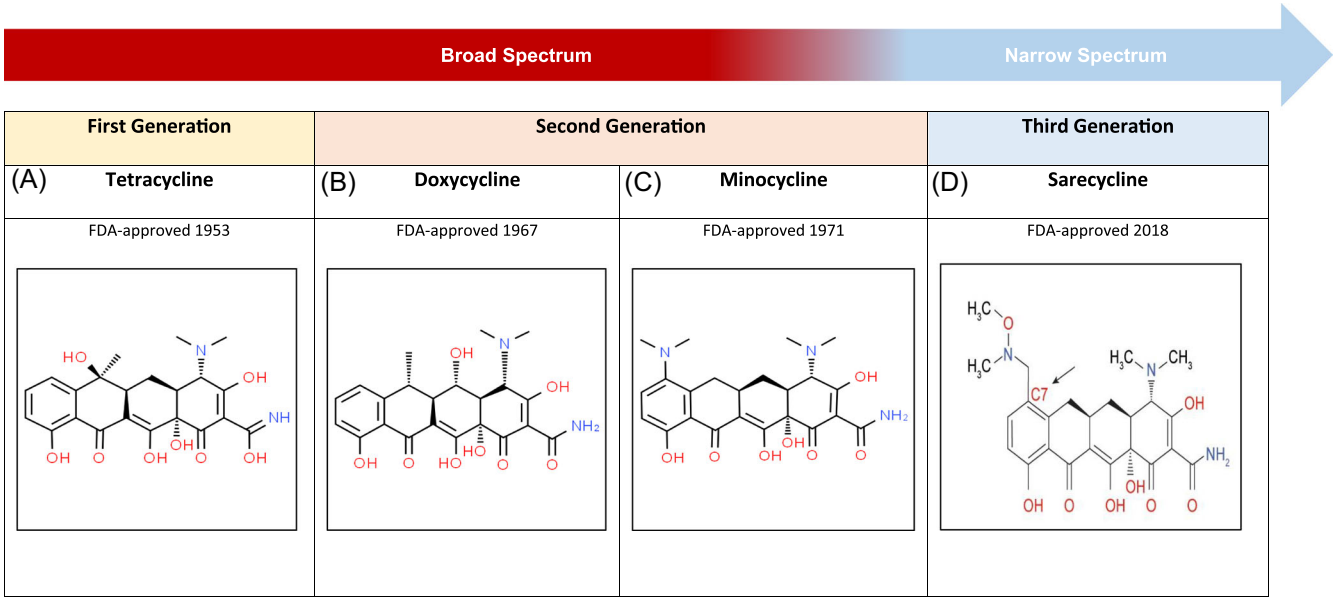


FIGURE 1 Chemical structures of the different tetracycline-class drugs use for the treatment of acne vulgaris. (A) Tetracycline. (B) Doxycycline. (C) Minocycline. (D) Sarecycline. The incorporation of a longer C7 moiety allows sarecycline to overcome tetracycline-resistant mechanisms mainly the efflux pump. *Structure image source*: http://www.chemspider.com/Chemical-Structure.28540486.html

were FDA-approved in 1967 and 1972, respectively. These semi-synthetic tetracyclines display broad-spectrum efficacy and are employed to treat a variety of infections as well as acne.[5] Sarecycline, the third-generation tetracycline, is a novel semisynthetic tetracycline compound with narrow-spectrum antimicrobial properties that was FDA-approved to treat acne in 2018. It has similar efficacy to other tetracyclines in acne treatment and with a low side-effect profile.[7] All members of the tetracycline family share a similar mechanism of action yet have differences in their spectrum of activity, the propensity to develop resistance, and their side-effect profile. The astute clinician should be well-versed in these differences to wisely choose the optimal antibiotic while also promoting antibiotic stewardship.[8]

3 | TETRACYCLINES FAMILY—MECHANISM OF ACTION

The tetracyclines combat two key factors in acne pathogenesis with their antimicrobial effect on *C. acnes* and their anti-inflammatory mechanisms.[4] Antimicrobial activity occurs by inhibition of protein synthesis in the bacterial cell (Figure 2). Specifically, tetracyclines reversibly bind to the 30S subunit of the bacterial ribosome, which prevents acyl-transfer RNA from binding to the ribosome.[5] Thus, protein synthesis is ceased which halts the growth and replication of the bacterial organism, producing a bacteriostatic effect. A recent study demonstrates that although sarecycline binds to the same part of the 30S ribosomal subunit as the other tetracycline members, sarecycline is unique in that it has a long C7 moiety that protrudes more toward the messenger RNA (mRNA)-binding channel and establishes a direct interaction with mRNA. This results in additional stabilization of sarecycline on the ribosome and confers sarecycline's superior inhibitory effect over other tetracyclines.[9] Additionally, this unique binding with mRNA may explain why sarecycline is able to overcome tetracycline resistance mechanisms.[9]

In addition to the presence of *C. acnes*, inflammation also drives acne pathogenesis and the tetracyclines can aid in inhibiting

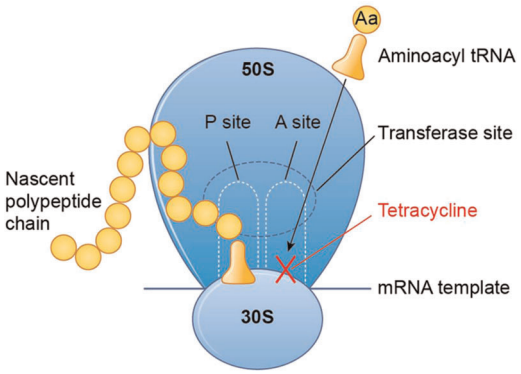


FIGURE 2 Mechanism of action of the tetracycline class of antibiotics. The tetracyclines reversibly bind to the 30S subunit of the bacterial ribosome, which prevents acyl-transfer RNA (tRNA) from binding to the ribosome.[5] Thus, protein synthesis is ceased which halts growth and replication of the bacterial organism, producing a bacteriostatic effect. A recent study demonstrates that although sarecycline binds to the same part of the 30S ribosomal subunit as the other tetracycline members, sarecycline is unique in that it has a long C7 moiety that protrudes more toward the messenger RNA (mRNA)-binding channel and establishes a direct interaction with mRNA

inflammation as well. As a class, over 10 different anti-inflammatory effects have been reported with the tetracyclines. The tetracyclines decrease the production and secretion of proinflammatory cytokines such as interleukin-1β (IL-1β), IL-8, and tumor necrosis factor-α. By inhibiting these cytokines, chemotaxis and activation of neutrophils are suppressed.[6] Tetracyclines also scavenge reactive oxygen species (ROS) and prevent oxidative damage to cellular macromolecules.[5] Additionally, the tetracyclines downregulate proteinases such as matrix metalloproteinases that contribute to acne formation.[10] It is because of these anti-inflammatory effects that some sub-antimicrobial dosages of tetracyclines, particularly doxycycline, have been shown to improve acne without exerting a bacteriostatic effect on *C. acnes*.[10]

Although all of the tetracyclines are mechanistically similar, they have important differences in their spectrum of activity and side-effect profiles, which impact how they are utilized clinically. Further below, we delve into each of the antibiotics in the tetracycline class starting with the most recently approved member, sarecycline, and ending with the oldest member, tetracycline.

4 | GUIDELINES FOR TREATING ACNE WITH ANTIBIOTICS

The American Academy of Dermatology 2016 consensus guidelines suggest oral antibiotics as a first-line treatment of moderate to severe acne.[4] Antibiotics should not be used as a monotherapy but instead with a topical retinoid and/or a benzoyl peroxide product. With adjunct use of other topical agents such as a retinoid and benzoyl peroxide, efficacy can be sustained even after the discontinuation of oral antibiotics. Furthermore, the duration of antibiotic use may be shortened if a topical retinoid and benzoyl peroxide are also employed. Second, the use of topical benzoyl peroxide prevents the development of bacterial resistance to antibiotics. This is achieved as benzoyl peroxide is bactericidal whereas most of the oral antibiotics used to treat acne have a bacteriostatic effect.[11] The AAD consensus guidelines suggest oral antibiotics use for the shortest period of time possible, ideally no more than 3–4 months. There is no consensus on whether oral antibiotics should be stopped abruptly or should be gradually reduced. Nonetheless, limiting the use of antibiotics is one key to reducing resistance.[4] There is also no guideline addressing retreatment with oral antibiotics for acne flares subsequent to the initial course of antibiotics. Patients who require longer treatment courses with oral antibiotics should be closely observed to limit use to the shortest possible duration.

5 | CONSEQUENCES OF ANTIBIOTIC RESISTANCE

The United Nations ad hoc Coordinating Group on Antimicrobial Resistance reported that by 2050, drug-resistant diseases could cause up to 10 million deaths each year and according to the Centers for Disease Control and Prevention,[12] more than 35,000 people currently die each year from antibiotic-resistant bacteria. The resulting damage to the economy would be detrimental and by 2030 antimicrobial resistance could force 24 million people into poverty.[13] The high use of antibiotics in acne treatment can result in an alteration of bacterial resistance patterns and the microbiome. Selection pressure or emergence of spontaneous mutations allow bacteria to develop resistance to antibiotics, meaning the bacteria can overcome the antimicrobial mechanism of action of the antibiotic. Once bacteria develop resistance to an antibiotic, treatment with the antibiotic will no longer be successful to combat infection. Antibiotic use may also promote bacterial resistance when the antibiotic is used for prolonged durations or if antibiotics are stopped and started repeatedly. Additionally, resistant bacteria can be spread person-to-person when in close proximity, such as between siblings.[14]

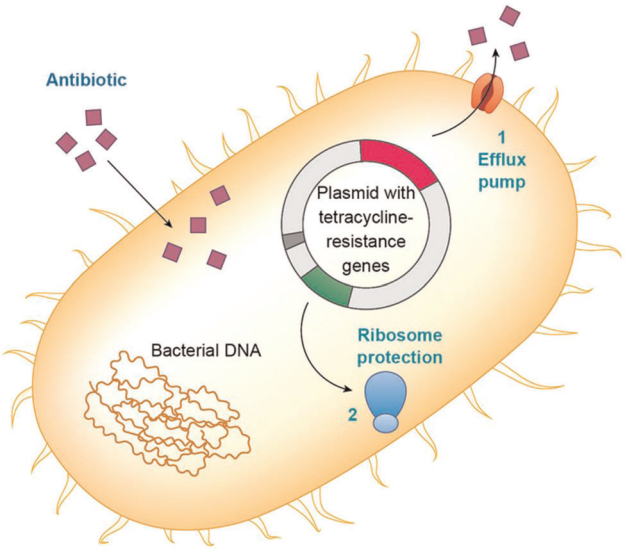


FIGURE 3 Bacterial mechanisms of resistance. Bacteria may develop resistance to the tetracycline class of antibiotics in two ways. (1) The bacteria may facilitate the removal of the antibiotic via the transmembrane efflux pump. (2) The bacteria may develop ribosomal protection mechanisms to prevent the tetracycline antibiotic from binding to the 30S ribosomal unit and exerting its effect

Although frequent and prolonged antibiotic exposure contributes to bacterial resistance, dissimilar antibiotic classes (i.e., tetracyclines, macrolides, and cephalosporins) and even different antibiotics within the same class (i.e., doxycycline, minocycline, and sarecycline) can have varying propensities for resistance.[15] For example, some classes of antibiotics are more likely to induce bacterial resistance than others and some specific antibiotics within the same class are more apt to cause bacterial resistance. The first tetracycline-resistant bacteria was identified in Japan over 40 years ago and in recent years, *C. acnes* resistance to tetracycline varies geographically from 2% to 30%.[16] Bacteria may develop resistance to the tetracycline-class antibiotics primarily by one of two main mechanisms: (a) Efflux pump and (b) ribosomal protection (Figure 3). The bacteria may increase the efflux of the antibiotic through its

transmembrane efflux pump, preventing the buildup of an inhibitory concentration of antibiotic in the cytoplasm. Alternatively, the bacteria may develop ribosomal protection mechanisms to prevent the tetracycline antibiotic from binding to the 30S ribosomal unit and exerting its effect.[17] Once a bacterium has developed such resistant mechanisms, it can spread these mechanisms to other bacteria by conjugal transfer of plasmids and transposons (Figure 4).[18]

Rising numbers of *C. acnes* resistant strains have been reported in all areas of the world. One study demonstrated that in the United States over 50% of *C. acnes* isolated from acne patients were resistant to doxycycline.[19–21] Resistance to doxycycline was correlated with failure to improve acne.[19] Along with treatment failure of acne, other implications of *C. acnes* resistance may include disruption of skin and gut microbiota, induction of opportunistic pathogens locally and systemically, and dissemination of drug-resistant strains to both healthcare providers and the general population.[22] Fortunately, newer generations of the tetracycline class such as sarecycline, demonstrate a lower propensity for development of bacterial resistance compared to the older members of the tetracycline class. *C. acnes* strains displayed a low likelihood for the development of resistance to sarecycline, with spontaneous mutation frequencies being 10^{-10} at 4–8× MIC (minimum inhibitory concentration).[23] Sarecycline also showed low spontaneous mutation frequencies ranging from 10^{-9} for *Staphylococcus aureus* and 10^{-8} for *Staphylococcus epidermidis* at fourfold and eightfold the MIC.[24] The chemical structure of sarecycline[25] allows it to be effective even against bacteria that have already developed resistance mechanisms to other tetracyclines[24] (Figure 1).

6 | NARROW- AND BROAD-SPECTRUM ANTIBIOTICS

Broad-spectrum antibiotics target a wide range of aerobic and anaerobic Gram-positive and -negative bacteria indiscriminately, whereas narrow-spectrum antibiotics are more pathogen-specific antibacterial agents.[26] The use of narrow-spectrum rather than broad-spectrum antibiotics may help to combat antibiotic resistance.[26] Currently, the most commonly prescribed antibiotics for acne are broad-spectrum antibiotics: tetracycline, doxycycline and minocycline. Development of resistance to broad-spectrum antibiotics extends to a wide array of pathogens, and not just the intended target. Using broad-spectrum antibiotics for acne could result not only in *C. acnes* that is resistant to antibiotics but also the development of gut bacteria and other bodily normal flora that are resistant to antibiotics. Spontaneous mutations may arise from exposure to the antibiotic and selection pressure allows the bacteria, which have developed mutations, to survive and replicate. The mutated genes can also be transferred to other pathogenic bacteria in close proximity, rendering them resistant as well.[17] For example, *C. acnes* that has developed tetracycline resistance genes may transmit these resistance genes to nearby Staphylococcal and Streptococcal bacteria.

By indiscriminately affecting gut bacteria as well as cutaneous bacteria, broad-spectrum antibiotics can cause an imbalance of normal microflora found in the gastrointestinal (GI) tract, a phenomenon known as gut dysbiosis. Although the use of broad-spectrum antibiotics is vital in the empirical treatment of some bacterial infections when the causative pathogen is not known, their impact on the gut microbiome cannot be ignored.[27] For example, even short-term (7-day) use of a broad-spectrum antibiotic can result in dysbiosis (i.e., an imbalance of the types of bacteria normally present) of the gut microbiome for up to 2 years after treatment and is associated with more adverse events than antibiotics.[8,13] Gut dysbiosis leads to increased susceptibility to infections, compromised immune system homeostasis, dysregulated metabolism, and the accumulation of antibiotic resistance (Figure 5).[15] The disruption of the healthy microflora provides the ideal habitat for infection by *Clostridium difficile*, which causes diarrhea and colitis.[16] Furthermore, broad-spectrum tetracycline antibiotics such as doxycycline have been associated with an increased risk of inflammatory bowel disease and inflammatory bowel syndrome.[28–30]

When choosing an oral antibiotic, one should consider the impacts that a broad-spectrum antibiotic has on both the development of resistant organisms and the implications of potentially inducing gut dysbiosis. Thus, the use of narrow-spectrum antibiotics is beneficial, particularly when the contributing pathogen is known, such as with acne vulgaris. Sarecycline, a narrow-spectrum antibiotic and a third-generation tetracycline, offers more targeted treatment to *C. acnes* without indiscriminately affecting normal flora in the gut and elsewhere. The use of narrow-spectrum antibiotics is one of the elements of antibiotic stewardship.

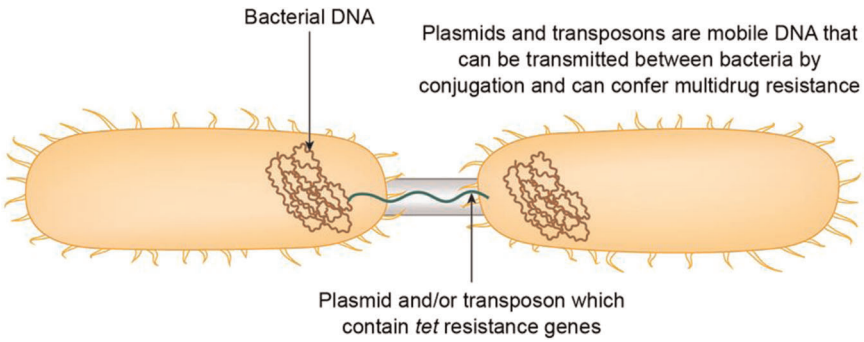


FIGURE 4 Bacterial spread of resistance. Bacteria can spread these mechanisms to other bacteria by conjugal transfer of plasmids and transposons

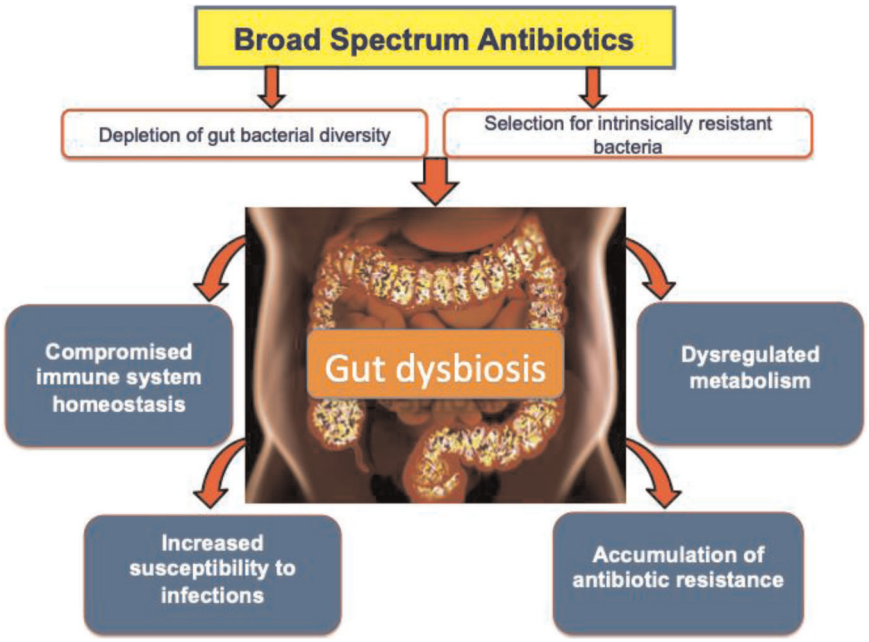


FIGURE 5 Consequences of broad-spectrum antibiotics and gut dysbiosis. Use of broad-spectrum antibiotics may cause depletion of gut bacterial diversity and selection for intrinsically resistant bacteria. These changes are referred to as gut dysbiosis. Gut dysbiosis can have many implications including compromised immune system homeostasis, increased susceptibility to infections, accumulation of antibiotic resistance, and a dysregulated metabolism

6.1 | Sarecycline

Sarecycline, the only third-generation tetracycline, is solely FDA-approved (2018) for treating moderate-to-severe inflammatory acne and was developed specifically as a narrow-spectrum tetracycline antibiotic for the treatment of acne.[23] To date, it is also the only oral tetracycline antibiotic that is approved for patients as young as 9 years old and is the only oral antibiotic with reported efficacy data on truncal acne. Dosing is weight-based (Table 1), once daily with or without food. It is an immediate-release formulation and once ingested, peak plasma concentration is reached in 1.5 to 2 h and is metabolized by the liver. The mean elimination half-life is 21 to 22 h and it is excreted 44.1% in urine and 42.6% in feces.[32] Coadministration with high-calorie, high-fat food decreased sarecycline absorption by 27%, but these changes were not considered clinically meaningful.[33] In an animal study, sarecycline showed a very low likelihood to cross the blood–brain barrier and this may explain the low rates of vestibular side effects observed in the clinical trials.[34–36]

Although no head-to-head studies exist with other oral antibiotics, some adverse events with sarecycline seem to be less-frequently reported than with other tetracyclines. A recently published systematic review for oral tetracycline antibiotics (sarecycline, minocycline, doxycycline, and tetracycline) in acne evaluated the efficacy and rates of adverse events for each of them.[37] In two identical Phase-3 clinical trials, GI side effects such as nausea and vomiting occurred in less than 5% of patients on sarecycline.[7] In a 40-week open-label safety clinical study on sarecycline for acne, the rates of GI treatment-emergent adverse events were nausea (2.1%), vomiting (1.9%), diarrhea (1.0%),[38] vulvovaginal candidiasis (0.8%), and vulvovaginal mycotic infection (0.6%).[23] Other adverse events commonly seen with tetracyclines such as phototoxicity and vestibular side effects occurred in less than 1% of patients on sarecycline (Table 2).[7,38] In the clinical trials, serum aminotransferase elevations were mild and no more frequent than with placebo. There were no instances of clinically apparent liver injury.[39] The safety profile for sarecycline is established for up to 1 year.[38] Like all of the tetracycline antibiotics, sarecycline is not safe for use during pregnancy due to the ability to cross the placenta and cause fetal harm.[23] Moreover, tetracyclines are not compatible with nursing as they are excreted through breast milk.[10]

The clinical efficacy of sarecycline in acne was assessed in two randomized, double-blinded, placebo-controlled, Phase 3 trials in a total of 2002 subjects of 9 years of age and older with moderate-to-severe acne.[16] Overall, 57% were female, 78% were Caucasian, 15% were Black or African American and 51% were adults (18–45 years of age).

Statistically significant improvement of inflammatory lesions with sarecycline has been demonstrated as early as 3 weeks.[7] For noninflammatory lesions, statistically significant efficacy was demonstrated by Week 6 in patient with 10 or more baseline noninflammatory lesions (post hoc pooled analysis).[7,33,40] In the first study, the mean change from baseline for inflammatory lesions at Week 12 was −52.2% for the sarecycline group and −35.2% for the placebo group ($p < .0001$). Similar efficacy results were shown in the second study.[7,23] Significant efficacy results on truncal acne (back and chest) were reported in both trials.[7]

A distinguishing characteristic of sarecycline is its narrow-spectrum activity compared to the broad-spectrum of activity exhibited by the other members of the tetracycline class.[24] Sarecycline has shown little to no activity against Gram-negative bacteria, such as the *Enterobacteriaceae*, which constitutes much of the normal flora of the GI tract. This may help reduce the deleterious effects of antibiotic treatment on the microbiome.[24,34] It is important to emphasize that despite the narrow range of activity,

TABLE 1 Tetracyclines[31]

Brand names	FDA-approved for acne	Recommended dose for acne	How supplied	Size (mg)	Notes
Tetracycline					
Achromycin	No[a]	250–500 mg po bid	Capsule	250 and 500	
Doxycycline					
Acticlate (doxycycline hyclate)	No[a]	50–100 mg po bid	Tablet	75 and 150	Tiny tablet to facilitate easier swallowing. Two scores so that it can be broken into thirds if needed.
Doryx (doxycycline hyclate)	No[a]	50–100 mg po bid	Tablet	50, 75, 100, 150, and 200	Delayed-release tablet with enteric coat
Vibramcyin (doxycycline hyclate)	No[a]	50–100 mg po bid	Capsule	100	
Periostat (doxycycline hyclate)	No	20 mg po bid	Tablet	20	For subantimicrobial use (i.e., anti-inflammatory, not antimicrobial)
Oracea (doxycycline hyclate)	No (approved for rosacea)	40 mg po qday	Capsule	40	For subantimicrobial use (i.e., anti-inflammatory, not antimicrobial). 30 mg immediate-release and 10 mg delayed-release
Minocycline					
Minocin	No[a]	50–100 mg po bid	Capsule	50 and 100	
Dynacin	No[a]	50–100 mg po bid	Capsule	50, 75, and 100	
Solodyn	Yes	Qday. Weight-based dosage chart	Tablet	55, 65, 80, 105, and 115	Extended-release
Ximino	Yes	Qday. Weight-based dosage chart	Capsule	45, 90, and 135	Extended-release
Sarecycline					
Seysara	Yes	Qday. Weight-based dosage chart	Tablet	60, 100, and 150	Immediate-release

Abbreviation: FDA, United States Food and Drug Administration.

[a]Listed as "adjunctive therapy for severe acne" in package insert.

TABLE 2 Comparison of tetracycline-class antibiotics used in acne vulgaris

	Can be taken with food	Lipophilic	Photosensitivity	GI upset	Vestibular adverse events	Spectrum of activity
Tetracycline	No	+	++	++	0[a]	Broad
Doxycycline	Yes	++	+++	+++	0[a]	Broad
Minocycline	Yes	+++	++	++	++	Broad
Sarecycline	Yes	++	0[a]	+	0[a]	Narrow

Abbreviation: GI, gastrointestinal.

[a]Occurs in less than 1% of patients.

sarecycline retains similar antibiotic activity as other tetracyclines against clinically relevant Gram-positives such as *C. acnes*.[8] In addition to the antibacterial activity, the chemical structure of sarecycline[25] allows the compound to overcome bacterial resistance mechanisms. As mentioned previously, modifications at C7 moiety were made to change bacterial ribosomal binding and minimize the ability for bacteria to develop resistance to sarecycline (Figure 2) This C7 moiety, the longest of any of the tetracyclines, protects against resistance by preventing efflux through the transmembrane pump and by protecting the ribosome from developing resistance mechanisms.[8,9,24,25] Low propensity to develop resistance to sarecycline has been demonstrated in *C. acnes*, *S. aureus*, and *S. epidermidis*.[24] Thus, sarecycline's narrow-spectrum activity and low propensity to induce spontaneous mutations may help not only combat antibiotic resistance in *C. acnes*, but also may offer a viable choice for antibiotic stewardship.[8]

6.2 | Minocycline

Unlike sarecycline, minocycline is a broad-spectrum antibiotic approved for acne in those 12 years of age and older. It is the most lipophilic member of the tetracycline family and because of its high lipid solubility, it easily crosses the blood–brain barrier.[41,42] This permeability into the brain results in more frequent vestibular side effects than other tetracyclines.[42] Minocycline dosing is often weight-based to reduce the vestibular side effects such as headache, dizziness, and vertigo. Standard minocycline has fivefold greater incidence of vestibular adverse events than extended-release minocycline.[43] As a result of its lipophilicity, minocycline has been postulated to have better penetration into the pilosebaceous gland than other tetracyclines, but this theory has never been proven to translate into superior clinical efficacy over other tetracyclines.

Due to the long half-life of 11–24 h, extended-release versions of minocycline are available and allow for once-daily dosing.[44] Absorption of minocycline is 95%–100% and it is not affected by food. Peak serum concentrations are reached in 1–4 h.[43,44] It is excreted 5%–12% through urine and 20%–35% through feces.[45] Both minocycline's lipophilicity and the presence of an amino side chain has been linked to a higher number of adverse events compared to other tetracyclines.[44] In fact, FDA data on adverse events estimate the rates with doxycycline to be around 13 per million, whereas with minocycline the rate is 72 per million.[45] With minocycline immediate release, central nervous system reactions (such as the vestibular side effects) were the most frequent adverse events (with studies ranging from <3% to 67%), followed by GI events. Discontinuations due to acute vestibular adverse events were reported in 1.7%–8.8% of patients.[42] In addition to the vestibular reactions, minocycline is unique among the tetracyclines in that it may also cause: skin hyperpigmentation, a serum sickness reaction, and drug-induced lupus.[45] Minocycline hyperpigmentation has been described as four clinically different types and may appear as blue-gray or brown macules in varying locations. It is sometimes more pronounced in sun-exposed areas, whereas in other cases the hyperpigmentation is present within scars or on mucosal surfaces.[46] A serum sickness reaction, a type-2 hypersensitivity reaction, may also rarely occur on minocycline. This reaction comprising of urticaria, fever, lymphadenopathy, and joint symptoms happens just days to a few weeks after initiating minocycline.[47] A drug-induced lupus-like syndrome has been described in patients on minocycline and is characterized by arthralgias, myalgias, elevated erythrocyte sedimentation rate, and the presence of antinuclear antibodies. It is seen most often with long-term (mean duration of 24 months) minocycline use.[48] Minocycline has also been associated with drug-induced hepatitis.[49,50] Minocycline is very rarely associated with the serious drug reaction known as the drug reaction with eosinophilia and systemic symptoms.[47]

Pseudotumor cerebri, also known as intracranial hypertension, has been reported with only the first- and second-generation tetracyclines (tetracycline, doxycycline, and minocycline). Marked by headaches and visual manifestations, it is treated by lumbar puncture. If not treated promptly, visual changes may be permanent. As psuedotumor cerebri has also been reported with isotretinoin use, it is not advised to take any of the tetracyclines concomitantly with isotretinoin.[51]

Two 12-week, randomized placebo-controlled trials utilizing extended-release minocycline have demonstrated efficacy in treating acne. In total, 615 subjects were treated with extended-release minocycline 1 mg/kg daily and compared with 309 subjects treated with placebo. In both studies, patients treated with minocycline had a significant mean percent reduction in inflammatory lesion count (43.1% and 45.8%) compared to placebo (31.7% and 30.8%). When graded utilizing an Evaluator's Global Severity Assessment scale, 16.6% of patient in the minocycline group had treatment success compared to 8.7% of patients in the placebo group.[52] Although proven to be effective in treating acne, minocycline is plagued by adverse events that distinguish it from the other tetracycline derivatives. Recent studies have shown that the use of minocycline in acne patients produces significant derangements in the microflora of the skin and gut, including many probiotic species.[27,53]

6.3 | Doxycycline

Like minocycline, doxycycline is another broad-spectrum antibiotic, yet with varying dosing options and a dissimilar side-effect profile. Doxycycline is often prescribed at a dose of 50–100 mg twice daily or 100 mg once daily for an antimicrobial effect (Table 1). However, a subantimicrobial dose of 20 mg twice daily or 40 mg once daily may be given which has been thought to exert anti-inflammatory effects with no antibacterial effect—based on small clinical studies.[54,55] This subantimicrobial dose is not FDA-approved for the treatment of acne. GI side effects are frequently reported with doxycycline use but may vary depending on the version and dosage of doxycycline that is prescribed. It is available for oral administration in two salt forms: doxycycline monohydrate and doxycycline hyclate with the latter also available as enteric-coated versions. Doxycycline monohydrate has a more basic pH and is more soluble in water than its hyclate counterpart.[56] Reported rates of GI upset are up to 53% with doxycycline monohydrate,[57] 40% with doxycycline hyclate, and 18% with enteric-coated doxycycline hyclate.[58] Unlike tetracycline, doxycycline can be taken with food to lessen GI distress such as nausea. Due to the acidity of the hyclate version of doxycycline, esophagitis is experienced more frequently with doxycycline hyclate than with doxycycline monohydrate.[59] Drug-induced esophageal injury has been reported with almost 100 different drugs and antibiotics have contributed to about 50% of cases and doxycycline alone to 27% of all cases.[59] To lessen the likelihood of esophagitis, patients are often advised to take doxycycline with a full glass of water and not to lie down for 1 hour after taking doxycycline. The potential may also exist for longer term side effects with doxycycline use as a large retrospective database study of acne patients revealed an association between doxycycline use and Crohn's disease (hazard ratio = 2.25; 95% confidence interval, 1.27–4.0).[28]

Phototoxicity reactions are another relatively common side effect of doxycycline. Although the frequency of phototoxicity depends on geographic location and doxycycline dosage, phototoxicity rates of those taking antimicrobial dosages of doxycycline are reported to be as high as 42% with those taking 200 mg/day.[60] With the lower anti-inflammatory dosages of doxycycline, the rates of phototoxicity are near zero.

The time to peak concentration in serum is 1.5–4 h for immediate release and 2.8–3 h for delayed-release with a half-life of 18–22 h. It is excreted 23%–40% through the urine and 30% through feces.[61] Benign intracranial hypertension is a rare side effect of doxycycline.

A placebo-controlled, randomized, crossover study of 62 patients evaluated the efficacy of doxycycline 100 mg po qday compared to placebo. Subjects were given doxycycline or placebo for 4 weeks, followed by a 4-week rest period, and then a second 4-week treatment period in which the medications were switched. Treatment with doxycycline resulted in a significant decrease in inflammatory lesion count (lesion count decreased by 26% in the first phase and 24% in the second phase). There was no significant reduction in inflammatory lesion count in those treated with placebo in either phase of the study.[62] A small placebo-controlled study ($n = 51$) investigating the efficacy of subantimicrobial dosing (20 mg po bid) showed a total reduction in lesions of 52% after 6 months of doxycycline compared to 18% with placebo.[10]

6.4 | Tetracycline

The oral broad-spectrum, first-generation, antibiotic, tetracycline, has been available for the treatment of acne since the 1950s. In recent years, there has been a short supply of tetracycline now with only one known manufacturer of the oral form.[63]

The recommended dose for acne in children and adolescents aged 9 and above includes a 500-mg dose twice daily (Table 1). Its use is hindered by the fact that it must be taken on an empty stomach, 1 h before or 2 h after meals to ensure adequate absorption. Due to the interference of aluminum and magnesium cations, tetracycline should be taken at least 1 to 2 h before or 4 h after antacid use. The half-life of tetracycline is 6–11 h and 30% is excreted through the urine and 20%–60% through feces.[61] Common adverse events include phototoxicity and GI upset. Teeth staining may occur if used in patients with developing teeth. Benign intracranial hypertension has been rarely reported with tetracycline.

Despite its shortcomings, tetracycline has demonstrated efficacy in treating acne. However, placebo-controlled studies are limited and small. One of the earlier tetracycline studies, a randomized, placebo-controlled, double-blind study of 51 acne patients, acne showed that 54% of patients on tetracycline improved compared to only 7% of those who received placebo ($p < .01$).[64] In another study, a statistically significant reduction in the acne severity grade was seen as early as 4 weeks in the oral tetracycline group compared to the placebo group.[65] Despite the studies demonstrating efficacy, its use is often marred by GI upset and phototoxicity.[31] Today's limited supply of tetracycline, the need to take it on an empty stomach, and its potential to cause GI upset and phototoxicity, make it less favorable.

7 | HOW TO CHOOSE WHICH TETRACYCLINE-CLASS DRUG TO USE?

The use of oral antibiotics is an important method of treatment for acne vulgaris and many oral antibiotics have proven to be effective in treating acne. Most evidence for efficacy in treating acne lies with the tetracycline class of antibiotics and most dermatologists will prescribe from this category with a minority choosing macrolide or cephalosporin antibiotics. Members of the tetracycline family of antibiotics are similar in that they have all been proven to be very effective for acne. However, tetracycline, doxycycline, minocycline, and sarecycline exhibit varying adverse events, pharmacokinetics, and antibiotic properties (Table 2). Before the introduction of sarecycline, most practitioners would select the use of doxycycline over tetracycline or minocycline. Tetracycline is in limited supply and must be taken on an empty stomach. Thus, it is not a practical option for many patients. Minocycline, though the most lipophilic agent, and theoretically, the best able to penetrate the pilosebaceous unit is often not the antibiotic of choice due to rare but serious adverse events. Doxycycline, long the most prescribed agent in the tetracycline class, has frequent adverse events such as nausea, esophagitis, and phototoxicity. Sarecycline, the newest option in the tetracycline class, has a low side-effect profile including GI adverse events such as nausea occurring in 2.1% of patients, vomiting in 1.9% and diarrhea in 1.0% reported in the Phase-3 open-label 40-week extension study, which is consistent with the results of the pivotal trials.[38] Phototoxicity was reported in less than 1% of patients and vestibular adverse events occurring in less than 1% of patients.[38] Both vulvovaginal mycotic infection and vulvovaginal candidiasis were reported in less than 1%.[23,38]

Antibiotic-resistant infections add considerable and avoidable costs to the already overburdened U.S. healthcare system. Studies have estimated that, in the United States, antibiotic resistance adds $20 billion in excess direct healthcare costs, with additional costs to society for lost productivity as high as $35 billion a year.[66] In an era of antibiotic stewardship, and when the causative pathogen is known, it is imperative to choose an antibiotic that has targeted activity to avoid disrupting the normal microflora and to limit the development of antimicrobial resistance. The use of broad-spectrum antibiotics may be unnecessary for skin conditions that are only associated with Gram-positive bacteria (such as acne vulgaris) if narrow-spectrum antibiotics are available. The use of broad-spectrum antibiotics to treat narrow-indication skin diseases such as acne contributes to the erosion of the antibiotic activity against clinically relevant Gram-negative bacterial infections for which few effective antibiotics are available.

Of all the antibiotics in the tetracycline class, sarecycline is the only narrow-spectrum antibiotic that can provide targeted antimicrobial activity against *C. acnes*. In summary, with dermatologists

being the highest prescriber of antibiotics out of all specialties, it is our duty to choose wisely the oral antibiotic that is not only effective but also poses the lowest risk to our patients and is consistent with antibiotic stewardship.

ACKNOWLEDGMENT

We appreciate the formatting of this manuscript provided by DerMEDit (www.dermedit.com).

CONFLICT OF INTERESTS

The author declares that there is no conflict of interests.

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How to cite this article: Graber EM. Treating acne with the tetracycline class of antibiotics: A review. *Dermatological Reviews*. 2021;2:321–330. https://doi.org/10.1002/der2.49