

Tetracyclines, Oral Review

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Tetracyclines, Oral Review

FDA-Approved Indications¹

Tetracyclines (with the exception of extended release dosage forms and doxycycline 20 mg tablets) are indicated for the treatment of the following infections:

- ◆ Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsial pox, and tick fevers caused by *Rickettsiae* species
- ◆ Respiratory tract infections caused by *Mycoplasma pneumoniae*
- ◆ Lymphogranuloma venereum caused by *Chlamydia trachomatis*
- ◆ Psittacosis (ornithosis) caused by *Chlamydia psittaci*
- ◆ Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence
- ◆ Inclusion conjunctivitis caused by *Chlamydia trachomatis*
- ◆ Uncomplicated urethral, endocervical, or rectal infections in adults caused by *Chlamydia trachomatis*
- ◆ Relapsing fever due to *Borrelia recurrentis*

Doxycycline is also indicated for the treatment of infections caused by the following Gram-negative microorganisms:

- ◆ Chancroid caused by *Haemophilus ducreyi*
- ◆ Plague due to *Yersinia pestis*
- ◆ Tularemia due to *Francisella tularensis*
- ◆ Brucellosis due to *Brucella* species (in conjunction with streptomycin)
- ◆ Bartonellosis due to *Bartonella bacilliformis*
- ◆ Granuloma inguinale caused by *Calymmatobacterium granulomatis*

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended. Tetracyclines are indicated for treatment of infections caused by the following Gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

- ◆ Respiratory tract infections caused by *Haemophilus influenzae*
- ◆ Respiratory tract and urinary tract infections caused by *Klebsiella* species

Tetracyclines are indicated for treatment of infections caused by the following Gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

- ◆ Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections:

- ◆ Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*
- ◆ Syphilis caused by *Treponema pallidum*
- ◆ Yaws caused by *Treponema pertenue*
- ◆ Actinomycosis caused by *Actinomyces israelii*

Tetracyclines

In addition to the indications above, the following table list specific indications for each of the tetracyclines.

Drug	Manufacturer	Indication(s)
demeclocycline ²	generic	Demeclocycline is indicated for the treatment of nongonococcal urethritis in adults caused by <i>Ureaplasma urealyticum</i> or <i>Chlamydia trachomatis</i> When penicillin is contraindicated, tetracyclines, including demeclocycline hydrochloride, are alternative drugs in the treatment of the following infections: <ul style="list-style-type: none"> ◆ Listeriosis due to <i>Listeria monocytogenes</i> ◆ Anthrax due to <i>Bacillus anthracis</i> ◆ Vincent's infection caused by <i>Fusobacterium fusiforme</i> ◆ Clostridial diseases caused by <i>Clostridium</i> species
doxycycline ^{3,4}	generic	Doxycycline is indicated for the treatment nongonococcal urethritis caused by <i>Ureaplasma urealyticum</i> . Doxycycline is also indicated for the treatment of infections caused by the following gram-negative microorganisms: <ul style="list-style-type: none"> ◆ Cholera caused by <i>Vibrio cholerae</i> ◆ <i>Campylobacter fetus</i> infections <p>Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended. Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:</p> <ul style="list-style-type: none"> ◆ <i>Escherichia coli</i> ◆ <i>Enterobacter aerogenes</i> ◆ <i>Shigella</i> species ◆ <i>Acinetobacter</i> species
doxycycline (Adoxa [®] TT, Adoxa [®] CK) ⁶	Doak Derm	Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug: <ul style="list-style-type: none"> ◆ Upper respiratory infections caused by <i>Streptococcus pneumoniae</i>
doxycycline monohydrate (Nutridox [™]) ⁷	Advanced Vision	When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections: <ul style="list-style-type: none"> ◆ Listeriosis due to <i>Listeria monocytogenes</i> ◆ Vincent's infection caused by <i>Fusobacterium fusiforme</i> ◆ Infections caused by <i>Clostridium</i> species <p>In severe acne, doxycycline may be useful adjunctive therapy</p> <p>Doxycycline is indicated for the prophylaxis of malaria due to <i>Plasmodium falciparum</i> in short-term travelers (<4 months) to areas with chloroquine and/or pyrimethaminesulfadoxine resistant strains. (Vibramycin[®])⁵</p> <p>Doxycycline 20 mg tablets are indicated for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.</p>
doxycycline delayed release (DR) (Oracea [®]) ⁸	Galderma	Treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients.

Drug	Manufacturer	Indication(s)
minocycline ⁹	generic	<p>Minocycline is indicated for the treatment of the following infections due to susceptible strains of the designated microorganisms:</p> <ul style="list-style-type: none"> ◆ Cholera caused by <i>Vibrio cholerae</i> ◆ Campylobacter fetus infections <p>When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:</p> <ul style="list-style-type: none"> ◆ Listeriosis due to <i>Listeria monocytogenes</i>. ◆ Anthrax due to <i>Bacillus anthracis</i> ◆ Vincent's infection caused by <i>Fusobacterium fusiforme</i> ◆ Infections caused by <i>Clostridium</i> species <p>Oral minocycline is indicated in the treatment of asymptomatic carriers of <i>Neisseria meningitidis</i> to eliminate meningococci from the nasopharynx. <i>Oral minocycline is not indicated for the treatment of meningococcal infection.</i></p> <p>Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by <i>Mycobacterium marinum</i>.</p>
minocycline extended release (ER) (Solodyn [®]) ¹⁰	generic, Medicis Derm	Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients > 12 years of age. Safety of use beyond 12 weeks has not been established.
tetracycline ¹¹	generic	<p>Tetracycline is indicated for :</p> <ul style="list-style-type: none"> ◆ Oral treatment of chronic bacterial conjunctivitis caused by susceptible organisms ◆ Treatment of skin and skin structure infections due to susceptible strains of <i>Staphylococcus aureus</i> and <i>S. pneumoniae</i>. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infection ◆ Prevention of acute exacerbations of chronic bronchitis ◆ Treatment of acne rosacea ◆ Treatment of inflammatory acne vulgaris ◆ Plague prophylaxis following exposure to <i>Yersinia pestis</i> although doxycycline is the treatment of choice for plague prophylaxis ◆ Eradication of <i>Helicobacter pylori</i> in the treatment of patients with duodenal ulcer disease (active or a history of duodenal ulcer)

Overview

The tetracyclines are antibiotics with similar antimicrobial spectra and safety profiles which are used for the treatment of a variety of infectious diseases. Increasing bacterial resistance to the tetracyclines and the development of newer antimicrobial agents have reduced the number of uses for the use of these drugs. Doxycycline remains a preferred antimicrobial for the treatment of various infections.

The 2006 Centers for Disease Control and Prevention (CDC) sexually transmitted diseases guidelines (STD) recommend doxycycline for the treatment of several infections.¹² Doxycycline is the preferred agent for the treatment of lymphogranuloma venereum, non-gonococcal urethritis, and cervicitis. Doxycycline or azithromycin, a macrolide, may be used for the treatment of non-gonococcal urethritis and cervicitis and *Chlamydia* infections, including those in children as young as eight years old. In April 2007, the CDC recommended cephalosporins be preferred agents for treatment of gonorrhea and pelvic inflammatory disease (PID) due to

increasing prevalence of fluoroquinolone-resistant gonorrhea throughout the United States. Newly updated oral regimens include intramuscular ceftriaxone plus doxycycline with or without oral metronidazole. Intramuscular cefoxitin plus oral probenecid plus doxycycline with or without metronidazole may also be considered. Doxycycline is a part of the treatment regimen for acute epididymitis and STD rectal infections when gonococcal and/or *Chlamydia* infections are presumed. Doxycycline and tetracycline are alternatives for the recommended treatment in syphilis when a patient has a severe penicillin allergy. Doxycycline is preferred over tetracycline due to the potential for greater gastrointestinal intolerance associated with tetracycline.

The joint guidelines from the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) published in 2007 recommend macrolides (e.g., erythromycin, clarithromycin, azithromycin – strong recommendation) or doxycycline (weak recommendation) for adult patients who are otherwise healthy without risk factors for multi-drug resistant *S. pneumoniae*.¹³ For adult outpatients with comorbidities including chronic heart, lung, renal, and hepatic disorders; diabetes; alcoholism; malignancies; asplenia; immunosuppression; or use of any antibiotic within the last three months or other risk factors for multi-drug resistant *S. pneumoniae*; first-line therapy may include a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) or a beta-lactam plus a macrolide as a strong recommendation. Beta-lactam selection may include high-dose amoxicillin or amoxicillin/clavulanate. Other beta-lactam alternatives include ceftriaxone, cefpodoxime, or cefuroxime. Doxycycline may be used as an alternative to macrolides in combination with a beta-lactam.

The CDC recommends ciprofloxacin or doxycycline for the initial treatment of inhalational anthrax.^{14,15,16} Other agents with *in vitro* activity suggested for use in conjunction with ciprofloxacin or doxycycline include rifampin, vancomycin, imipenem, chloramphenicol, penicillin and ampicillin, clindamycin, and clarithromycin; other than for penicillin, limited or no data exist regarding the use of these agents in the treatment of inhalational *B. anthracis* infection. Cephalosporins and trimethoprim/sulfamethoxazole should not be used for therapy. Prophylaxis for inhalational anthrax exposure should include ciprofloxacin or doxycycline for 60 days as first-line agents. High-dose penicillin (e.g., amoxicillin or penicillin VK) may be an option for antimicrobial prophylaxis when ciprofloxacin or doxycycline are contraindicated. Because of potential adverse effects of prolonged use of ciprofloxacin or doxycycline in children, amoxicillin was an option for completion of the remaining 60 days of therapy for persons infected in the bioterrorist attacks of 2001. Clinical data are very limited for the treatment of anthrax in infants and children. For cutaneous anthrax, ciprofloxacin and doxycycline also are first-line therapy for adults and children.

In the treatment of acne vulgaris, the 2007 guidelines from the American Academy of Dermatology state that systemic antibiotics including tetracyclines (recommendation grade A – consistent and good quality patient-oriented evidence; grade 1 - good quality patient-oriented evidence) are a standard of care in the management of moderate and severe acne and treatment-resistant forms of inflammatory acne.¹⁷ According to the guidelines, doxycycline and minocycline are more effective than tetracycline. For eradication of *Propionibacterium acnes*, there is some evidence that minocycline is superior to doxycycline. Other systemic antibiotics mentioned for the management of moderate to severe acne include erythromycin, trimethoprim, and trimethoprim/sulfamethoxazole.

Pharmacology¹⁸

The tetracyclines are bacteriostatic. They exert their antimicrobial effect by reversibly binding to the 30S subunit of the bacterial ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis and thus cell growth. Tetracyclines are active against a wide range of Gram-positive and Gram-negative organisms and have similar antimicrobial spectra; cross-resistance is common.

Doxycycline and minocycline, both long-acting, are more lipid-soluble and have minimal renal clearance, making these two agents drugs of choice in patients with compromised renal function.

Minocycline has been shown to have in vitro activity against *Propionibacterium acnes*, an organism associated with acne; however, the clinical significance of this in patients with acne is unknown.

Demeclocycline antagonizes the actions of vasopressin at the collecting duct in the nephron. The clinical use of demeclocycline is limited to treatment of Syndrome of Inappropriate Antidiuretic Hormone (SIADH).¹⁹

Spectrum of Activity

The tetracyclines are active against Gram-positive and Gram-negative bacteria. Doxycycline is typically active against *Bacillus anthracis*, *Listeria monocytogenes*, and *S. aureus*, although tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection. The tetracyclines are unreliable against streptococcal infections, as resistance rates have been reported to be 50 percent. Use of any tetracycline for a streptococcal infection should be guided by culture and sensitivity data. Doxycycline is typically effective against the following Gram-negative organisms: *Bartonella bacilliformis*, *Brucella species*, *Calymmatobacterium granulomatis*, *Campylobacter fetus*, *Francisella tularensis*, *Haemophilus ducreyi*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Vibrio cholerae*, and *Yersinia pestis*. Culture and sensitivity data for other Gram-negative organisms should be consulted. Most of the *Rickettsia* bacteria are susceptible to the tetracyclines. Tetracycline is commonly used in combination with bismuth salts and metronidazole plus acid suppression therapy in the treatment of *H. pylori*.

Pharmacokinetics²⁰

Drug	Half-life (hrs)	Elimination (%)
demeclocycline	10-17	Urine: 42 Feces: 42
doxycycline ^{21,22}	18-22	Doxycycline is excreted in the urine and feces as unchanged drug.
doxycycline (Adoxa TT, Adoxa CK) ²³	16.33	
doxycycline delayed release (DR) (Oracea) ²⁴	21.2	
doxycycline monohydrate (Nutridox) ²⁵	n/a	
minocycline	11-22	Partially metabolized
minocycline extended release (ER) (Solodyn) ²⁶	n/a	Renal: 4-19 Feces: reported
tetracycline	6-12	Urine: 60 Feces: reported

n/a = not available

Contraindications/Warnings^{27,28,29,30,31,32,33}

Doxycycline, minocycline, and tetracycline are contraindicated in any persons with hypersensitivity to tetracycline.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of eight years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used in this age group, except for anthrax, including inhalational anthrax (post-exposure), unless other drugs are not likely to be effective or are contraindicated.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including the tetracycline class, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.

Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

The plasma concentrations of doxycycline (Oracea) achieved during administration are less than the concentration required to treat bacterial diseases. *In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina. The Oracea dosage form of doxycycline should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.

Serious liver injuries, including irreversible drug-induced hepatitis, and fulminant hepatic failure (sometimes fatal) have been reported in post-marketing reports with minocycline use for the treatment of acne.

Central nervous system (CNS) adverse effects including dizziness, vertigo, and lightheadedness may occur with minocycline. Patients experiencing CNS adverse effects should be cautioned about driving vehicles and using hazardous machinery while on minocycline. The symptoms may disappear during therapy and usually rapidly disappear until discontinuation of minocycline.

Doxycycline syrup (Vibramycin Syrup) contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Administration of demeclocycline has resulted in appearance of the diabetes insipidus syndrome (polyuria, polydipsia, and weakness) in some patients on long-term therapy. The syndrome has been shown to be nephrogenic, dose-dependent, and reversible on discontinuance of therapy. Patients who are experiencing CNS symptoms associated with demeclocycline therapy should be cautioned about driving vehicles or using hazardous machinery while on demeclocycline therapy.

Drug Interactions^{34,35,36,37,38,39,40}

Tetracyclines as a class have been shown to increase levels of anticoagulants (monitor INR for warfarin patients). Concurrent use of a tetracycline may render oral contraceptives less effective. Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin. Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations. Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline. The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity. Increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.

Reports of pseudotumor cerebri (benign intracranial hypertension) have been associated with the concomitant use of isotretinoin and tetracyclines. Since both oral retinoids, including isotretinoin and acitretin, and the tetracyclines, primarily minocycline, can cause increased intracranial pressure, their concurrent use should be avoided.

Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage when on concurrent minocycline (Solodyn) therapy.

Adverse Effects^{41,42,43,44,45,46,47}

The following adverse effects have been reported in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, increases in liver enzymes, and hepatic toxicity (including hepatitis and liver failure)

With minocycline, additional hepatic adverse effects have included hyperbilirubinemia, hepatic cholestasis, and jaundice. Hepatitis, including autoimmune hepatitis, and liver failure have been reported with minocycline use.

Due to virtually complete absorption of oral doxycycline and oral minocycline, adverse effects of the lower bowel, particularly diarrhea, have been infrequent. With minocycline, stomatitis, dysphagia, and enamel hypoplasia have been reported.

Instances of esophageal ulcerations have been reported in patients receiving oral tetracyclines. Most of the patients were reported to have taken the medication immediately before lying down.

Skin: Maculopapular and erythematous rashes, erythema multiforme

Exfoliative dermatitis has been reported but is uncommon. Fixed drug eruptions and Stevens-Johnson syndrome have been reported rarely. Lesions occurring on the glans penis have caused balanitis. Pigmentation of the skin and mucous membranes has also been reported. Photosensitivity can occur. With minocycline, alopecia, erythema nodosum, hyperpigmentation of nails, pruritus, toxic epidermal necrolysis, and vasculitis have been reported.

Renal toxicity: Acute renal failure.

Rise in BUN has been reported and is apparently dose-related. Nephrogenic diabetes insipidus has been reported.

Tetracyclines

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, lupus-like syndrome, pulmonary infiltrates with eosinophilia

Hematologic: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

With minocycline, agranulocytosis and pancytopenia have been reported.

CNS: Pseudotumor cerebri (benign intracranial hypertension) in adults, dizziness, headache, tinnitus, visual disturbances, and myasthenic syndrome

With minocycline, convulsions, headache, sedation, vertigo, hypesthesia, tinnitus, decreased hearing, and paresthesia have also been reported.

Musculoskeletal: With minocycline, arthralgia, arthritis, bone discoloration, myalgia, joint stiffness, and joint swelling have been reported

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Very rare cases of abnormal thyroid function have been reported.

Tooth discoloration has occurred in pediatric patients less than eight years of age and also has been reported rarely in adults.

Special Populations^{48,49,50,51,52,53,54}

Pediatrics

Use of tetracycline products in children less than eight years of age is not recommended due to the potential for tooth discoloration. Safety and effectiveness of minocycline ER (Solodyn) in children less than 12 years of age have not been established.

Pregnancy

All agents in this class are Pregnancy Category D.

Nursing Mothers

The American Academy of Pediatrics considers ciprofloxacin and tetracyclines including doxycycline to be usually compatible with breastfeeding because the amount of drug absorbed by infants is small, but little is known about the safety of long-term use.⁵⁵ Mothers concerned about the use of ciprofloxacin or doxycycline for antimicrobial prophylaxis should consider expressing and then discarding breast milk so that breastfeeding can be resumed when antimicrobial prophylaxis is completed. Decisions about antimicrobial choice and continuation of breastfeeding should be made by the mother and her and the infant's healthcare providers.

Renal Impairment

If renal impairment is present, minocycline (Solodyn) doses may need to be adjusted to avoid excessive systemic accumulation of the drug and possible liver toxicity.

Dosages

Drug	Usual Dosing	Availability
demeclocycline ⁵⁶	<p>Adults: 150 mg four times daily or 300 mg twice daily</p> <p>Gonorrhea patients sensitive to penicillin: initial oral dose of 600 mg followed by 300 mg every 12 hours for four days to a total of 3 g</p> <p>Pediatrics > 8 years: 7-13 mg/kg/day depending on severity of disease, divided into two to four doses, not to exceed dosage of 600 mg daily</p>	150, 300 mg tablets
doxycycline ^{57,58,59,60}	<p>Adults: 100 mg twice daily for most infections; duration of therapy is typically seven to 10 days, but duration may depend on severity of infection</p> <p>Inhalational anthrax: 100 mg twice daily for 60 days</p> <p>Prophylaxis of malaria: 100 mg daily beginning one to two days before travel and continuing for four weeks after leaving malarious area</p> <p>Dental: 20 mg twice daily at 12-hour intervals, usually in the morning and evening</p> <p>Pediatrics > 8 years and < 45 kg: 2.2 mg/kg give twice daily on Day 1, then 2.2 mg/kg daily</p> <p>If > 45 kg, then use adult dosing</p> <p>Prophylaxis for malaria: 2 mg/kg once daily (not to exceed 100 mg)</p>	<p>50, 75, 100, 150 mg capsules</p> <p>75, 100 mg delayed release capsules</p> <p>20, 50, 75, 100, 150 mg tablets</p> <p>75, 100, 150 mg delayed release tablets</p> <p>25 mg/5mL, 50 mg/5mL suspension</p> <p>Adoxa TT Kit = 30 doxycycline 150 mg tablets plus 30 cleansing pads</p> <p>Adoxa CK Kit = 60 doxycycline 150 mg tablets plus 60 cleansing pads</p>
doxycycline DR (Oracea) ⁶¹	<p>Adults: One capsule daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals.</p>	40 mg capsules with 30 mg immediate release and 10 mg delayed release beads
minocycline (Solodyn) ⁶²	<p>Adults:</p> <p>44-54 kg: 45 mg daily</p> <p>55-77 kg: 65 mg daily</p> <p>78-102 kg: 90 mg daily</p> <p>103-125 kg: 115 mg daily</p> <p>126-136 kg: 135 mg daily</p> <p>Swallow whole, do not crush chew or split tablets. May be taken with or without food.</p>	45, 65, 90, 115, 135 mg extended release tablets

Dosages (continued)

Drug	Usual Dosing	Availability
minocycline ⁶³	<p>Adults: 200 mg initially followed by 100 mg every 12 hours or two or four 50 mg pellet-filled capsules may be given initially followed by one 50 mg capsule 4 times</p> <p>Pediatrics: 4 mg/kg initially followed by 2 mg/kg every 12 hours, not to exceed the usual adult dose</p> <p>Minocin pellet-filled capsules may be taken with or without food. Swallow whole.</p>	<p>50, 100 mg pellet-filled capsules</p> <p>50, 75, 100 mg capsules</p> <p>50, 75, 100 mg tablets</p>
tetracycline ⁶⁴	<p>Adults: 250-500 mg every six hours or 500-1,000 mg every 12 hours. Duration of therapy dependent on type and severity of infection.</p> <p>Acne rosacea: 250-1,500 mg per day</p> <p>Inflammatory acne vulgaris: 125-250 mg every six hours then taper to 125-500 mg daily or every other day.</p> <p>Pediatrics: 4 mg/kg initially followed by 2 mg/kg every 12 hours, not to exceed the usual adult dose</p>	<p>250, 500 mg capsules</p>

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to reduce the risk of esophageal irritation and ulceration.⁶⁵ If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Clinical TrialsSearch Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Much of the comparative literature within the class was published 20 to 30 years ago. Comparative literature for the tetracycline class was performed in the 1970's and 1980's. In the treatment of acne, minocycline was found to provide a more rapid response than tetracycline in two double-blind studies.^{66,67} In another study, minocycline had superior antibacterial action and

reduced incidence of bacterial resistance in acne patients compared to tetracycline.⁶⁸ In an earlier double-blind study, minocycline 50 mg twice daily and tetracycline 250 mg twice daily had similar efficacy in the treatment of acne vulgaris.⁶⁹

Doxycycline and tetracycline were compared in a small study of 24 patients with ocular rosacea.⁷⁰ Efficacy, based on subjective measures by the patients, was greater with tetracycline ($p=0.041$) at six weeks; however, after three months of treatment, symptoms scores were similar in both groups. Gastrointestinal adverse effects occurred more frequently with tetracycline (37.5 percent) than with doxycycline (12.5 percent).

More recently, the tetracyclines have been compared in open-label trials to agents in other drug classes such as azithromycin, tazarotene, oxytetracycline, benzoyl peroxide, and topical erythromycin.^{71,72,73}

The newer extended release dosage forms of doxycycline DR (Oracea) and minocycline ER (Solodyn) have been only compared to placebo in published literature.^{74,75}

Meta-Analysis

A systematic review of the evidence of minocycline in the treatment of acne vulgaris identified randomized controlled trials of minocycline for acne vulgaris.⁷⁶ Articles were identified by searching the following electronic databases; MEDLINE, EMBASE, Biosis, Biological Abstracts, International Pharmaceutical Abstracts, Cochrane Skin Group's Trial Register, Theses Online, BIDS ISI Science Citation Index, National Research Register, Current Controlled Trials, and BIDS Index to Scientific and Technical Proceedings. A total of 27 randomized controlled trials met the inclusion criteria and were included. The comparators used were placebo (two studies), oxytetracycline (one), tetracycline (six), doxycycline (seven), lymecycline (two), topical clindamycin (three), topical erythromycin/zinc (one), cyproterone acetate/ ethinyloestradiol (one), oral isotretinoin (two), topical fusidic acid (one), and there was one dose response study. The trials were generally small and of poor quality and in many cases the published reports were inadequate. Although minocycline was shown to be an effective treatment for acne vulgaris, in only two studies was it found to be superior to other tetracyclines. Both of these were conducted under open conditions and had serious methodological problems. A third study showed it to be more effective than 2% fusidic acid, applied topically, against inflammatory lesions in mild to moderate acne. Differences in the way adverse drug reactions were identified could have accounted for the wide variation between studies in numbers of events reported. This meant that no overall evaluation could be made of incidence rates of adverse events associated with minocycline therapy. Minocycline is likely to be an effective treatment for moderate acne vulgaris, but no reliable trial evidence exists to justify its use as first-line therapy. Its efficacy and safety relative to other acne therapies could not be reliably determined due to the poor methodological quality of the trials and lack of consistent choice of outcome measures.

Summary

Tetracyclines are used in the treatment of a variety of infections in adults and children over age of eight years. Tetracycline is indicated in the management of *H. pylori* in combination with other medications including other antibiotics and acid suppression therapies. Adverse effects common to the tetracyclines include gastrointestinal complaints and risk for esophageal ulceration.

Doxycycline is the antibiotic of choice among the tetracyclines for infections involving the upper respiratory tract, sexually transmitted diseases, and the urogenital tract (prostatitis, cervicitis, and urethritis). Doxycycline possesses unique characteristics such as a broad spectrum of activity, a long serum half-life, superior tissue penetration, and excellent oral absorption which contribute to its clinical superiority over tetracycline. The drug is not eliminated by the kidneys as is tetracycline and is therefore the drug of choice when a tetracycline is indicated in patients with renal dysfunction and in hemodialysis patients. Doxycycline is also a preferred agent to prevent inhalational anthrax after confirmed or suspected aerosol exposure to *B. anthracis*.

Specific dosage forms and indications of a few of the tetracyclines are now available. Doxycycline DR (Oracea) is only indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adults. It does not have a significant effect for generalized erythema of rosacea and has not been evaluated for treatment of erythematous, telangiectatic, or ocular components of rosacea or in the prevention and treatment of infections. Minocycline ER (Solodyn) is indicated for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris. Comparative literature for these agents is lacking. Doxycycline 20 mg tablets (Periostat) are indicated as adjunctive therapy to scaling and root planning in reducing pocket depths and increasing periodontal attachment levels in patients with periodontal disease.

Demeclocycline is used infrequently for the treatment of infections. The clinical use of demeclocycline is limited to treatment of SIADH. In a limited number of trials, demeclocycline has been effective in the treatment of water intoxication and inappropriate antidiuretic hormone secretion. When compared with tetracycline, demeclocycline is associated with a higher incidence of phototoxicity.

References

- ¹ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ² Declomycin [package insert]. Coral Gables, FL; Glades Pharmaceuticals; June 2007.
- ³ Vibramycin [package insert]. New York, NY; Pfizer; April 2007.
- ⁴ Periostat [package insert]. Newtown, PA; Collagenex; March 2004.
- ⁵ Vibramycin [package insert]. New York, NY; Pfizer; April 2007.
- ⁶ Adoxa [package insert]. Melville, NY; PharmaDerm; March 2008.
- ⁷ Nutridox [package insert]. Woburn, MA; Advance Vision Research; 2010. Available at: <http://www.nutridox.net/rx.html>. Accessed February 22, 2010.
- ⁸ Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; May 2008.
- ⁹ Minocin [package insert]. Cranford, NJ; Triax Pharmaceuticals; May 2008.
- ¹⁰ Solodyn [package insert]. Scottsdale, AZ; Medicis; December 2009.
- ¹¹ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ¹² Center for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2006. MMWR. 2006; 55(RR-11); 1-100. Available at: <http://www.cdc.gov/std/treatment/2006/pid.htm>. Accessed on February 22, 2010.
- ¹³ Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis. 2007; 44(Suppl 2):S27-S72. Available at: <http://www.journals.uchicago.edu/doi/pdf/10.1086/511159?cookieSet=1>. Accessed February 22, 2010.
- ¹⁴ CDC. Available at: <http://emergency.cdc.gov/agent/anthrax/treatment/>. Accessed February 22, 2010.
- ¹⁵ CDC. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm>. Accessed February 22, 2010.
- ¹⁶ CDC. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5045a5.htm>. Accessed February 22, 2010.
- ¹⁷ Strauss JS, Krowchuk DP, Leyden JJ, et al for the American Academy of Dermatology. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007; 56(4):651-63.
- ¹⁸ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ¹⁹ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ²⁰ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ²¹ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ²² Periostat [package insert]. Newtown, PA; Collagenex; March 2004.
- ²³ Adoxa [package insert]. Melville, NY; PharmaDerm; March 2008.
- ²⁴ Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; May 2008.
- ²⁵ Nutridox [package insert]. Woburn, MA; Advance Vision Research; 2010. Available at: <http://www.nutridox.net/rx.html>. Accessed February 22, 2010.

- ²⁶ Solodyn [package insert]. Scottsdale, AZ; Medicis; December 2009.
- ²⁷ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ²⁸ Adoxa [package insert]. Melville, NY; PharmaDerm; March 2008.
- ²⁹ Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; May 2008.
- ³⁰ Nutridox [package insert]. Woburn, MA; Advance Vision Research; 2010. Available at: <http://www.nutridox.net/rx.html>. Accessed February 22, 2010.
- ³¹ Periostat [package insert]. Newtown, PA; Collagenex; March 2004.
- ³² Solodyn [package insert]. Scottsdale, AZ; Medicis; December 2009.
- ³³ Vibramycin [package insert]. New York, NY; Pfizer; April 2007.
- ³⁴ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ³⁵ Adoxa [package insert]. Melville, NY; PharmaDerm; March 2008.
- ³⁶ Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; May 2008.
- ³⁷ Nutridox [package insert]. Woburn, MA; Advance Vision Research; 2010. Available at: <http://www.nutridox.net/rx.html>. Accessed February 22, 2010.
- ³⁸ Periostat [package insert]. Newtown, PA; Collagenex; March 2004.
- ³⁹ Solodyn [package insert]. Scottsdale, AZ; Medicis; December 2009.
- ⁴⁰ Vibramycin [package insert]. New York, NY; Pfizer; April 2007.
- ⁴¹ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ⁴² Adoxa [package insert]. Melville, NY; PharmaDerm; March 2008.
- ⁴³ Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; May 2008.
- ⁴⁴ Nutridox [package insert]. Woburn, MA; Advance Vision Research; 2010. Available at: <http://www.nutridox.net/rx.html>. Accessed February 22, 2010.
- ⁴⁵ Periostat [package insert]. Newtown, PA; Collagenex; March 2004.
- ⁴⁶ Solodyn [package insert]. Scottsdale, AZ; Medicis; December 2009.
- ⁴⁷ Vibramycin [package insert]. New York, NY; Pfizer; April 2007.
- ⁴⁸ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ⁴⁹ Adoxa [package insert]. Melville, NY; PharmaDerm; March 2008.
- ⁵⁰ Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; May 2008.
- ⁵¹ Nutridox [package insert]. Woburn, MA; Advance Vision Research; 2010. Available at: <http://www.nutridox.net/rx.html>. Accessed February 22, 2010.
- ⁵² Periostat [package insert]. Newtown, PA; Collagenex; March 2004.
- ⁵³ Solodyn [package insert]. Scottsdale, AZ; Medicis; December 2009.
- ⁵⁴ Vibramycin [package insert]. New York, NY; Pfizer; April 2007.
- ⁵⁵ American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108:776-89.
- ⁵⁶ Declomycin [package insert]. Coral Gables, FL; Glades Pharmaceuticals; June 2007.
- ⁵⁷ Adoxa [package insert]. Melville, NY; PharmaDerm; March 2008.
- ⁵⁸ Vibramycin [package insert]. New York, NY; Pfizer; April 2007.
- ⁵⁹ Periostat [package insert]. Newtown, PA; Collagenex; March 2004.
- ⁶⁰ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ⁶¹ Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; May 2008.
- ⁶² Solodyn [package insert]. Scottsdale, AZ; Medicis; December 2009.
- ⁶³ Minocin [package insert]. Cranford, NJ; Triax Pharmaceuticals; May 2008.
- ⁶⁴ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ⁶⁵ Available at: www.clinicalpharmacology.com. Accessed February 22, 2010.
- ⁶⁶ Samuelson JS. An accurate photographic method for grading acne: initial use in a double-blind clinical comparison of minocycline and tetracycline. *J Am Acad Dermatol*. 1985; 12(3):461-7.
- ⁶⁷ Hubbell CG, Hobbs ER, Rist T, et al. Efficacy of minocycline compared with tetracycline in treatment of acne vulgaris. *Arch Dermatol*. 1982; 118(12):989-92.
- ⁶⁸ Eady EA, Cove JH, Holland KT, et al. Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. *Br J Dermatol*. 1990; 122(2):233-44.
- ⁶⁹ Cullen SI, Cohan RH. Minocycline therapy in acne vulgaris. *Cutis*. 1976; 17(6):1208-10, 1214.
- ⁷⁰ Frucht-Pery J, Sagi E, Hemo I, et al. Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol*. 1993; 116(1):88-92.
- ⁷¹ Akhyani M, Ehsani AH, Ghiasis M, et al. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of rosacea: a randomized open clinical trial. *Int J Dermatol*. 2008; 47(3):284-8.
- ⁷² Leyden J, Thiboutot DM, Shalita AR, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. *Arch Dermatol*. 2006; 142(5):605-12.
- ⁷³ Ozolins M, Eady EA, Avery AJ, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomized controlled trial. *Lancet*. 2004; 364(9452):2188-95.
- ⁷⁴ Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol*. 2007; 56(5):791-802.
- ⁷⁵ Fleischer AB Jr, Dinehart S, Stough D, et al. Safety and efficacy of a new extended-release formulation of minocycline. *Cutis*. 2006; 78(4 Suppl):21-31.
- ⁷⁶ Garner SE, Eady EA, Popescu C, et al. Minocycline for acne vulgaris: efficacy and safety. *Cochrane Database Syst Rev*. 2003; (1):CD002086.