

ROSACEA MEDICAL MANAGEMENT GUIDELINES



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Objectives

(1) Provide an overview of the fundamental disease state of rosacea and quality of life implications

(2) Outline available pharmacologic treatments for rosacea with reference to supporting research and literature

- The pharmacologic agents discussed are inclusive of those that are Food and Drug Administration (FDA)-approved based on phase III pivotal trials, commonly used agents based on extensive clinical experience, and less commonly used alternatives reported in peer-reviewed literature.

Disease State Fundamentals

- Rosacea is a common facial disorder presenting most commonly in adulthood, estimated to affect ~14 million Americans.^{1,2} The disorder is chronic and is characterized by intermittent periods of exacerbation.
- Clinical signs of rosacea include central facial erythema, inflammatory lesions (papules, pustules) and telangiectasias.¹⁻³
- The underlying cause of rosacea is unknown, however, several pathophysiologic associations have been reviewed in the literature.^{1,3-6}
- Major pathogenic components appear to be inflammatory, vascular and neural in origin. There is no definitive evidence that rosacea is caused by a microbial pathogen, such as a bacterium, parasite or virus.^{1,3-6}
- The most common clinical presentations of cutaneous rosacea include the inflammatory (papulopustular) and erythematotelangiectatic subtypes. Other presentations include phymatous rosacea (such as rhinophyma) and granulomatous rosacea. Ocular rosacea is not uncommon in patients with cutaneous rosacea; clinical presentations of ocular rosacea include conjunctivitis, blepharitis, stye formation and keratitis.¹⁻³

Quality of Life Implications

- Rosacea has been shown to exhibit a negative impact on quality of life. Surveys conducted by the National Rosacea Society have shown that approximately 70% of rosacea patients experience lower self-confidence and lower self-esteem as a result of their condition, with 41% of patients avoiding public contact or canceling social engagements.⁷ Furthermore, among patients with severe rosacea, approximately 70% claim that their disorder has had a negative effect on their professional relationships, and nearly 30% have missed work as a result of their condition.⁷
- Effective treatment for rosacea has been correlated with marked improvement in quality of life indices.⁷

Pharmacologic Treatment of Rosacea: Topical Therapy

Sulfacetamide 10%-Sulfur 5%

- FDA-approved product labeling supports the indication for rosacea treatment based on drug efficacy study implementation (DESI) drug designation.
- Multiple randomized vehicle-controlled and comparative studies, both blinded and open-label, have confirmed efficacy and safety in patients with inflammatory rosacea measured as marked reduction in inflammatory lesions and erythema.⁸⁻¹¹
- Multiple vehicle formulations are available including cleanser, cream, gel, and topical suspension.

Metronidazole

- Approved by the FDA for inflammatory rosacea based on phase III

- pivotal trials (double-blind, randomized, vehicle-controlled studies).
- Multiple, blinded, split-face, and open-label vehicle-controlled studies have been completed supporting the efficacy and safety of both topical metronidazole 0.75% and 1% formulations, including gel, cream and lotion.⁸⁻¹³
- Both gel and cream formulations of 1% strength are available and FDA-approved for application once daily. Three formulations of the 0.75% strength are available including gel, lotion and cream, FDA-approved for twice daily use.

Azelaic Acid

- Approved by the FDA based on phase III pivotal trials of 15% gel formulation (double-blind, randomized, vehicle-controlled studies).
- Efficacy and safety supported by multiple blinded and vehicle-controlled trials evaluating 15% formulation applied twice daily.^{8,10,14,15}

Miscellaneous Topical Agents

- Other alternative topical agents have been reported to be effective based on small studies and case reports.^{8,9}
- Conflicting results have been reported with topical calcineurin inhibitors (tacrolimus, pimecrolimus) used for treatment of rosacea, with efficacy demonstrated in some cases and little benefit or exacerbation noted in others.¹⁶⁻¹⁹
- Data supporting use of topical clindamycin or erythromycin for rosacea is very limited.^{9,10} Relative lack of data compared to other available topical therapies, and concern regarding emergence of antibiotic resistance (especially with chronic use) suggest that topical erythromycin or clindamycin are not generally recommended for treatment of rosacea.
- Topical benzoyl peroxide 5%-clindamycin 1% has been shown to be effective for inflammatory rosacea.^{20,21}
- Topical antiparasitic agents, such as permethrin, have been shown to be effective in case reports of refractory rosacea that were diagnosed as demodicidosis (*Demodex folliculitis*).^{22,23}
- Topical retinoid therapy suggested as beneficial for rosacea, although supporting data is very limited.^{8,9}

Pharmacologic Treatment of Rosacea: Oral Therapy

Anti-Inflammatory Agents

- Doxycycline 40mg controlled-release formulation (anti-inflammatory dose doxycycline), administered as one capsule daily, is FDA-approved for treatment of inflammatory rosacea in adults based on phase III pivotal trials demonstrating efficacy and safety.
- Anti-inflammatory dose doxycycline (administered once daily) is not categorized by the FDA as an antibiotic, is devoid of antimicrobial activity based on microbiologic and pharmacokinetic studies

completed over up to 18 months, and is unique in its bioavailability profile as compared to other doxycycline formulations.²⁴⁻²⁶ Anti-inflammatory dose doxycycline does not exert antibiotic selection pressure and thus does not induce antibiotic resistance; its mechanism of action in rosacea appears to relate to the anti-inflammatory and biologic activities of doxycycline.^{24,25}

- Anti-inflammatory dose doxycycline is the only systemic therapy approved by the FDA for treatment of rosacea.^{24,25}

Antibiotic/Anti-Inflammatory Agents

- Tetracycline agents, including tetracycline, doxycycline ($\geq 50\text{mg/day}$), and minocycline exhibit both antibiotic and anti-inflammatory activities.²⁶⁻³⁰
- The use of tetracycline, minocycline, and doxycycline (other than anti-inflammatory dose doxycycline), although not FDA-approved for treatment of rosacea, are utilized based on extensive clinical experience and peer-reviewed literature including some clinical trials.^{8,9,26}
- Other oral antibiotic/antimicrobial agents that have been used for treatment of rosacea in case reports and small studies are metronidazole and some macrolide antibiotics.^{8,9}
- The more recent emergence of concerns regarding antibiotic resistance among government agencies, such as the FDA and Centers for Disease Control (CDC), physician organizations, and the lay public, have prompted recommendations that antibiotic use be limited as much as possible, and directed against a bacterial pathogen when present.³¹⁻³⁴ The lack of data supporting a bacterial component definitively related to the pathogenesis of rosacea suggests overall that medical therapies which are anti-inflammatory in nature are best considered for initial treatment of rosacea, especially the inflammatory (papulopustular) subtype, with oral antibiotic agents used in cases that are poorly responsive to a reasonable trial of topical therapy and/or oral anti-inflammatory therapy.

Isotretinoin

- Oral isotretinoin has been reported to be effective for severe and/or refractory cases of rosacea; low-dose and intermittent therapy may be helpful in selected cases.^{35,36}
- Appropriate precautions such as pregnancy avoidance in female patients, and recommended clinical and laboratory monitoring, such as blood testing of serum lipids are recommended. All patients receiving oral isotretinoin must be registered in and compliant with the iPledge program.

Skin Care Recommendations

- Patients with rosacea characteristically exhibit sensitive skin; baseline signs and symptoms prior to therapy commonly include dryness, scaling, stinging, burning, and pruritus.^{1-4,15,37}
- Appropriate skin care, including use of a gentle cleanser and moisturizer, and photoprotection, including sunblock/sunscreen use, are important components of daily skin maintenance in rosacea, and are significant adjuncts to pharmacologic therapy.^{8,9,38-41}

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