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Ophthalmic Technology Assessment

# Oral Antibiotics for Meibomian Gland-Related Ocular Surface Disease

## *A Report by the American Academy of Ophthalmology*

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***Objective:*** To review the existing medical literature on the role of oral antibiotics in the management of ocular surface disease (OSD) that arises from disorders of the meibomian glands and to assess the efficacy of oral antibiotics in the management of this common ocular disease.

***Methods:*** A literature search was last conducted on August 12, 2015, in the PubMed and Cochrane databases for English-language original research investigations that evaluated the role of doxycycline, minocycline, and azithromycin in OSD among adult patients. The searches identified 87 articles, and 8 studies ultimately met the criteria outlined for this assessment.

***Results:*** The 8 studies identified in the search documented an improvement in meibomian gland-related OSD after treatment with these agents, although side effects were common. This search identified only 1 randomized, controlled trial to assess the efficacy of these medications.

***Conclusions:*** Although oral antibiotics are used commonly in the management of OSD, there is no level I evidence to support their use. There are only a few studies that have assessed the efficacy of oral antibiotics in clinically meaningful ways in the management of OSD that arises from disorders of the meibomian glands. The current level of evidence is insufficient to conclude that antibiotics are useful in managing OSD arising from disorders of the meibomian glands. The few existing studies on the topic indicate that oral antibiotics may be an effective treatment for OSD that results from meibomian gland disease. *Ophthalmology 2016;123:492-496 © 2016 by the American Academy of Ophthalmology.*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Oculoplastics and Orbit Panel is to analyze the usefulness of oral antibiotics in the management of ocular surface disease (OSD).

## Background

Ocular surface disease ensues in part from an insufficient or unstable tear film and may result in degradation of the surface of the eye with subsequent pain, irritation, blurred vision, photophobia, and vision loss.[1] This disease is one of the most common reasons for visits to ophthalmologists[2] and reportedly affects 15% of Americans older than 65 years.[3] Often, the impact of these symptoms is quite severe, and OSD represents a significant cost burden and impediment to normal quality of life for patients who experience it.[4–6]

Although OSD is relatively common and often symptomatic, this disorder largely is incurable.[7,8] Ocular surface disease may arise from several possible causes, and damage to the ocular surface represents a final common pathway for a diversity of pathologic processes. Multiple therapies have been used to address OSD, including topical compresses, topical lubrication and immunomodulation, nutritional supplementation, oral antibiotics, laser and light-based therapies, and surgical interventions. Despite the wide array of available treatment options, OSD often is difficult to treat and may be refractory to these interventions.

Meibomian gland-related diseases result in an unstable tear film with subsequent OSD, and matrix metalloproteinases, collagen production, interleukin 1, nitric oxide, and activated B cells all play a role in the inflammatory component of OSD. Both in vitro and in vivo studies have



http://dx.doi.org/10.1016/j.ophtha.2015.10.062
ISSN 0161-6420/15

shown that doxycycline, minocycline, and azithromycin modulate the expression of these inflammatory mediators.[9–11] Furthermore, the tetracycline class of drugs is thought to decrease meibomian gland dysfunction.[12] Based on these effects, oral antibiotics have been prescribed to treat meibomian gland-related OSD, and these agents often are a first-line therapy for this specific variant of OSD.[13,14] In light of the common nature of meibomian gland-related OSD and the difficulty in treating this persistent, widespread problem, the panel reviewed the existing literature to determine the clinical impact of oral doxycycline, minocycline, and azithromycin in OSD management.

## Question for Assessment

The objective of this assessment was to address the following question: Do oral antibiotics improve the health of the ocular surface, signs of OSD, or OSD-related symptoms among patients with dry eye disease, OSD, or both that result from meibomian gland-related diseases?

## Description of Evidence

A literature search was conducted last on August 12, 2015, in the PubMed and Cochrane Library databases and included the search terms *doxycycline*, *minocycline*, *azithromycin*, *ocular surface disease*, *ocular surface diseases*, *dry eye disease*, *dry eye diseases*, *dry eye syndrome*, *dry eye syndromes*, *meibomian gland*, *meibomian glands*, *meibomian gland dysfunction*, *blepharitis*, *rosacea*, *rosaceous*, *ocular pemphigoid*, *keratitis sicca*, *keratoconjunctivitis sicca*, and *Sjögren's syndrome*. Articles were limited to original research in which an English language abstract was available and those in which participants consisted of patients with meibomian gland-related OSD who were 18 years of age or older, treated with oral antibiotics, and followed up for at least 1 month. Acceptable outcome measures included changes in the score on a standardized questionnaire used for measuring OSD severity (e.g., the Ocular Surface Disease Index, Allergan, Inc., Parsippany, NJ), visual acuity, standardized scoring of keratitis or OSD, or the requirement for other medications (e.g., artificial tears, topical cyclosporine).

Of 87 articles retrieved, 35 were selected for full-text review; of these, 11 were included for abstraction. Based on this abstraction, 3 articles were rejected from final inclusion because the metrics used by the authors did not explore variables that were related directly to clinical outcomes (i.e., these articles were focused on biophysical parameters such as matrix metalloproteinase concentrations or cytologic outcomes). Consequently, 8 articles were used in the final analysis. The panel's methodologist (E.A.B.) evaluated the quality of these studies. Well-conducted randomized controlled trials were graded as level I evidence. Well-conducted case-control or cohort studies, as well as lower-quality randomized controlled trials, were graded as level II evidence, and case series and lower-quality case-control and cohort studies were rated as level III evidence. Based on this review, 2 articles were graded level II and 6 articles were graded level III.

## Published Results

The 8 articles[15–22] that were included in the final data set explored the effects of doxycycline, minocycline, and azithromycin on ocular surface disease.

### Effect of Doxycycline on Meibomian Gland-Related Ocular Surface Disease

Yoo et al[15] (level II) randomly divided 150 patients with meibomian gland disease into 3 equally sized groups and initiated 1-month courses of doxycycline at a dose of either 200 mg twice daily or 20 mg twice daily, or a placebo. Patients were masked to the treatment they received. As compared with the placebo group, the groups of patients who received doxycycline showed significant improvements in their tear film breakup times and Schirmer test scores. The authors did not identify any significant differences in these 2 outcomes between the 2 different doses of doxycycline. Six patients (6%) who took doxycycline (4 patients [8%] in the high-dose group and 2 patients [4%] in the low-dose group) discontinued its use because of side effects, including gastrointestinal disorders, cutaneous pruritus, urticaria, and cutaneous lesions. This study did not specifically assess the change in the degree of blepharitis among patients taking doxycycline.

Iovieno et al[16] (level III) prescribed doxycycline to 8 patients with blepharitis at a dose of 100 mg twice daily for 2 weeks, followed by a course of this dose on a once-daily basis for an additional 2 weeks. The investigators scored each patient's ocular surface signs and symptoms according to a novel standardized grading system at baseline, and after 4 weeks of treatment, the scores of both parameters improved significantly. Three patients experienced nausea and 1 patient developed a facial rash.

Quarterman et al[17] (level III) studied 39 patients with ocular rosacea and treated them with doxycycline at a dose of 100 mg daily for 12 weeks; 33 patients completed the study. At the end of the 12-week course, the patients experienced a statistically significant improvement in their tear film breakup times and Schirmer test results. Additionally, the authors documented a significant improvement in eyelid inflammatory signs after treatment with doxycycline. Three patients experienced gastrointestinal side effects that precluded completion of the study. Changes in the degree of keratitis and visual acuity were not reported.

Sobolewska et al[18] (level III) administered 40 mg oral doxycycline (as a combination of 30 mg of immediate-release medication and 10 mg of delayed-release medication) to 15 patients with ocular rosacea for a mean of 8 months. Although the degree of severe keratitis and the visual acuity did not improve with this regimen, 86.7% of patients experienced resolution or significant improvements in subjective complaints of ocular surface disease-related symptoms and blepharitis. After completion of the course of doxycycline, the degree of conjunctival redness was rated as absent or mild in all patients. One patient discontinued the use of doxycycline after 5 months because of a reported mild stomach ache.

### Effect of Minocycline on Meibomian-Gland Ocular Surface Disease

Lee et al[19] (level II) performed a randomized, prospective trial to assess the impact of minocycline on 60 patients with meibomian

gland dysfunction. In this trial, the investigators assessed Ocular Surface Disease Index scores, tear film breakup time, Schirmer testing, fluorescein staining, and biomicroscopic eyelid margin and meibomian gland evaluations in patients assigned to receive either artificial tears or artificial tears and minocycline (dosed at 50 mg twice daily for 2 months). Patients taking minocycline experienced statistically significant improvements in all metrics and enjoyed a greater degree of improvement in tear film breakup time, fluorescein staining score, eyelid margin health, and meibum quality than those patients who were assigned to receive only artificial tears. Nonetheless, 2 patients were forced to discontinue the use of minocycline because of gastrointestinal side effects. Although this study was designed as a randomized controlled trial, the methodology did not describe withdrawals from the study, did not include an intent-to-treat strategy, nor did it provide masking, and the study was thus graded as level II evidence.

Aronowicz et al[20] (level III) sought to determine the effect of minocycline on 16 patients with meibomitis via an observational prospective trial. Patients initially were treated with 50 mg minocycline daily for 2 weeks, followed by 10 weeks of 100 mg daily, and the investigators used a grading system that assessed the appearance of the eyelids, degree of meibomian gland plugging, amount of secretion, and presence of conjunctival erythema. Additionally, they assessed tear volume, corneal staining score, amount of tear evaporation, and Schirmer testing score. These metrics were evaluated after 3 months of treatment and 3 months after the completion of treatment. Although the authors did not detect an improvement in corneal staining or Schirmer test results, patients experienced improvements in eyelid margin thickening and vascularization scores, a decrease in eyelid margin debris, and less meibomian gland obliteration, and these effects were durable after the cessation of the medication.

### Effect of Azithromycin on Meibomian-Gland Ocular Surface Disease

In a prospective, noncontrolled case series, Igami et al[21] (level III) assessed the effects of oral azithromycin (3 cycles of 500 mg/day for 3 consecutive days with 7-day intervals) in 13 patients with posterior blepharitis who did not to respond to topical antibiotics and corticosteroids. Thirty days after completion of the course of medication, the authors evaluated tear film breakup time, Schirmer test results, fluorescein and rose Bengal staining scores, and an eyelid scoring system that measured the severity of eyelid debris, telangiectasias, mucous secretion, and eyelid margin edema and erythema. Although corneal staining scores did not improve, the authors reported a statistically significant improvement in tear film breakup time, and with the exception of eyelid edema, all clinical metrics were statistically significantly improved with the use of oral azithromycin. One patient experienced gastrointestinal side effects, but completed the course of treatment.

Similarly, Bakar et al[22] (level III) administered oral azithromycin (500 mg/day for 3 consecutive days, weekly for 4 weeks) in patients with papulopustular rosacea, and evaluators conducted symptom questionnaires and used eyelid and cornea plus conjunctival standardized scoring systems. Additionally, Schirmer test results, tear film breakup time, and fluorescein and rose Bengal measurements were assessed. At a 4-week evaluation, patients experienced 87%, 40%, and 31.9% improvements in symptom, eyelid, and conjunctival scores, respectively. Despite these improvements, the changes in Schirmer test results, tear film breakup time, and corneal staining scores were not statistically significant.

## Discussion

Few studies have explored the clinical effects of oral antibiotics on meibomian gland-related ocular surface disease. The literature search identified only 8 studies that met inclusion criteria, and these investigations consisted of 2 level II studies and 6 level III studies. Nonetheless, although these studies were not designed to evaluate multiple clinically meaningful metrics, they suggest that oral antibiotics may be useful in the management of OSD that arises from meibomian gland disorders. Each study demonstrated a therapeutic benefit for the outcomes that were assessed, although corneal staining generally remained stable. Indeed, although there is a relative paucity of data to support the common use of oral antibiotics to treat meibomitis-related OSD, the studies that we identified document improvements both in clinical symptoms and the health of the tear film. Of course, although oral antibiotics seem to be a useful agent in the management of OSD, clinicians should be aware that these medications may be useful only in the setting of changes to the ocular surface that emanate from diseases of the meibomian glands, and these results cannot be generalized to other variants of OSD that arise from other causes.

Despite the dearth of experimental clinical evidence to support their use, oral antibiotics are used widely in the management of OSD. In fact, several review articles[13,14,23] describe these agents as a mainstay of OSD care. The potential benefits of oral antibiotics in OSD are supported by nonclinical experimental evidence. Smith et al,[24] Fernandez-Robrero et al,[10] and Ataie-Kachoie et al[25] demonstrated a dramatic reduction in matrix metalloproteinase levels after treatment with each of these antibiotics at a variety of anatomic sites. Similarly, in a murine model of dry eye disease, Zhang et al[26] documented decreased OSD after treatment with doxycycline. Liu et al[27] recently reported that azithromycin induced the differentiation of cultured immortalized human meibomian gland cells and improved lipid production. Determination of the applicability and clinical significance of these basic science findings awaits further study.

As with any therapeutic intervention, the potential benefits of oral antibiotics need to be considered carefully relative to the possible risks inherent to their use. The side-effect profile of antibiotics has been well documented previously and includes dermatologic complications (including photosensitivity and the development of lesions), gastrointestinal complications (emesis, diarrhea, dyspepsia), and hypersensitivity.[15] Notably, doxycycline use is contraindicated in children and in women who are pregnant or nursing. Additionally, Stevens-Johnson syndrome has been reported after the use of each of these agents,[28–32] and the use of each of these antibiotics may result in supratherapeutic international normalized ratio results among patients taking warfarin.[33,34] Recent evidence also indicates that chronic antibiotic use may affect the human microbiome, resulting in systemic complications.[35] Although these medications

generally are well tolerated, patients and clinicians should be aware of possible problems that may arise with systemic antibiotics. In the studies identified in this analysis, 0% to 8% of patients were unable to tolerate oral antibiotic treatment.

## Conclusions

Ocular surface disease remains difficult to treat. The existing literature provides only scant evidence that oral antibiotics may be beneficial in the management of meibomian gland-related OSD. Additional research is needed to determine if there is a role for doxycycline, minocycline, and azithromycin to treat this common, recalcitrant condition.

The difficulty in treating OSD underscores the requirement to identify useful therapies. Given that oral antibiotics are used commonly as therapeutic agents in OSD, future investigations should explore meticulously the role of these medications in the management of this disorder. Specifically, this assessment demonstrated that the existing literature failed to use clinically meaningful parameters. The absence of such documentation certainly does not indicate that oral antibiotics do not have benefit in the treatment of OSD, but the current literature does not definitively demonstrate a benefit in using these therapies.

Future investigations may wish to use existing scoring systems to assess the impact of oral antibiotics on OSD. Specifically, patient-directed questionnaires (i.e., the Ocular Surface Disease Index) may be useful to assess the effect of these medications carefully.[36] Additionally, standardized grading systems of OSD and keratopathy could be used to delineate the changes that occur with the use of antibiotics. Finally, methodologically sound randomized trials are necessary to provide assurance that oral antibiotics have a positive impact on OSD.

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## Footnotes and Financial Disclosures

Originally received: October 28, 2015.
Final revision: October 28, 2015.
Accepted: October 28, 2015.
Available online: December 23, 2015. Manuscript no. 2014-1894.

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Prepared by the Ophthalmic Technology Assessment Committee Oculoplastics and Orbit Panel and approved by the American Academy of Ophthalmology's Board of Trustees June 26, 2015.

Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Funded without commercial support by the American Academy of Ophthalmology.

Abbreviations and Acronyms:
**OSD** = ocular surface disease.

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