Put Dry Eye Treatment Where Your Patient’s Mouth Is

These oral medications may help treat your dry eye patients when drops aren’t enough. By Paul M. Karpecki, O.D.

Many of us primarily consider topical medications to treat dry eye disease. At times, however, alternative treatments, particularly oral medications, may be of greater benefit for patients who have ocular surface disease. This article explores the oral medications that can help patients who have dry eye disease and related conditions, such as Sjögren’s syndrome.

Oral Tetracyclines

Oral tetracyclines—tetracycline, doxycycline and minocycline—treat ocular surface disease by inhibiting the formation of cytokines, such as interleukin-1 (IL-1), and damaging enzymes, such as matrix metalloproteinase-1 (MMP-1) and MMP-3. Cytokines are inflammatory mediators. MMP is an enzyme implicated in corneal damage, including recurrent erosion.

Oral tetracyclines are especially effective in patients who have lid diseases, such as blepharitis and meibomianitis. They should be prescribed if topical treatments fail or if patients have severe inflammation of the lids or ocular surface.

Medications in this group include Sumycin (tetracycline, Apotheon) 250mg q.i.d., Vibramycin (doxycycline, Pfizer) 100mg or 50mg b.i.d. and Minocin (minocycline, Wyeth) 100mg q.d. or b.i.d. These oral tetracyclines usually work best when prescribed at a higher dose first (e.g., b.i.d. for doxycycline) and then tapered after a minimum of one to two months of treatment.

Doxycycline decreases the bioactivity of major inflammatory cytokines, which partially explains the anti-inflammatory properties of this medication. Most clinicians have found doxycycline to be the most effective oral tetracycline in ocular disease management, and that it typically causes the fewest side effects at a dose of 50mg b.i.d. Although doxycycline can be administered at 100mg b.i.d., this increased dose appears to offer little added benefit, yet it causes an increase in side effects.

Side effects. Side effects of tetracyclines include gastrointestinal upset (e.g., gastritis and esophagitis), yeast infections and photosensitivity. Advise patients taking tetracyclines to wear protective clothing and sunscreen to prevent the increased risk of sunburn.

To minimize the risk of gastritis, which is the primary reason patients discontinue their medication, prescribe a 50mg dose rather than 100mg. Or, consider prescribing Periostat (doxycycline hyclate, CollaGenex Pharmaceuticals), which contains 20mg of doxycycline (see “Can Gum Disease Drug Fight Dry Eye?” on page 38).

Oral medications may help patients who have irregular corneal surfaces.
To further reduce stomach upset, tell patients to drink a full glass of water with the medication. This prevents the tablets from getting lodged in the esophagus, which can result in esophagitis. Also, tell patients to take their first tablet with breakfast and the second tablet with dinner. Tetracycline and minocycline should not be taken with milk or dairy products (see below). Advise patients not to take a tablet immediately before bedtime, as lying down may cause acid reflux.

Some additional side effects: Minocycline can cause vestibular toxicity in higher doses.1 Also, patients who take tetracycline medications are at risk for developing pseudotumor cerebri, although the risk is lower with doxycycline and minocycline than with tetracycline.2 Patients on long-term therapy should undergo liver enzyme testing annually. Medications taken long-term require testing of the organ through which they are metabolized.

There has been some concern of a link between tetracycline medications and breast cancer. However, research suggests that doxycycline may actually prevent tumor formation.3 One study found that doxycycline significantly enhanced tumor regression activity in mice. The study concluded that doxycycline taken in combination with cyclophosphamide may lead to additional improvements in breast cancer treatment.4

Interactions. Tetracyclines become ineffective when taken with dairy products and antacids because the calcium chelates the medication.5 Specifically, studies have shown that tetracyclines form insoluble complex molecules by metal ion chelation when patients take various antacids or vitamins that contain iron. This interaction can cause tetracycline absorption to decrease by more than 90%.6

Doxycycline has less of a tendency for chelation than other tetracycline medications. Even so, advise patients not to take tetracyclines for at least two hours after a meal that contains dairy products. Also, educate your patients about not taking antacids because they are likely to take them if they experience gastritis as a side effect.

Contraindications. Tetracyclines incorporate into tissues that are calcifying.7 Do not prescribe them for children because they may cause tooth discoloration and bone development problems.8 Pregnant women and nursing mothers should also avoid taking tetracyclines because there is a potential for craniofacial, bone and tooth deformities in the fetus.9

Omega-3 Fatty Acids and Nutritional Supplements

Gamma-linolenic acid (GLA) and alpha-linolenic acid are the primary fatty acids of plant products, such as flaxseed. The primary omega-3 fatty acids of fish oil are eicopentanoic acid (EPA) and docosahexaenoic acid (DHA).

Studies have shown that GLA and fish oils are useful in treating Sjogren’s syndrome, mild to moderate dry eye and dry eye related to rosacea.10,11 This is likely because omega-3 fatty acids have anti-inflammatory capabilities. Omega-3 fatty acids, particularly fish oils, are also important in retinal development, prevention of age-related macular degeneration and cardiovascular disease, and decreased incidence of cataract formation.12,13,14 Omega-3 fatty acids can be
prescribed early in the course of dry eye treatment.

Diets rich in core vitamins—such as vitamins A, B6 and C, potassium and zinc—may be necessary for normal tear function. I would recommend these as well as omega-3 fatty acid supplements for patients whose diets lack these.

**Contraindications.** Although omega-3 fatty acids, especially fish oils, can be beneficial to fetal development in pregnant women, some fish are contaminated with methylmercury. So, pregnant women should observe the government’s advisories regarding certain fish and use of fish oil supplements.

**Oral Secretagogues**

The two primary systemic secretagogues that have shown efficacy in treating dry mouth and dry eye are Evoxac (cevimeline, Daiichi Pharmaceuticals) and Salagen (pilocarpine, MGI Pharma).16,17

Oral Evoxac was approved for the treatment of dry mouth in patients who have Sjögren’s syndrome. The drug’s primary function is to augment salivary flow rates, but it has also been shown to improve dry eye symptoms.18 In one study, 60 patients were divided into three groups. One group received a placebo, another group received 20mg of Evoxac t.i.d., and the third group received 30mg of Evoxac t.i.d. for four weeks.19 Patients who took the 20mg dose t.i.d. experienced improved tear flow and reduced corneal and conjunctival staining. Although a larger sample size is necessary to confirm these findings, a dose of 20 or 30mg t.i.d. is recommended for patients who have Sjögren’s syndrome.

**Side effects.** Side effects tend to be mild. They include excessive sweating, nausea, runny nose, excessive saliva, stomach pain, sinus inflammation, fatigue and hot flashes.20

**Contraindications.** Patients who have uncontrolled asthma, acute iritis, and narrow-angle or angle-closure glaucoma should not use Evoxac.20

Oral Salagen is used to treat dry eye and dry mouth in patients who have conditions such as radiation-induced xerostomia. One study examined the effects of Salagen on 373 patients with Sjögren’s syndrome. Patients were randomized into three groups: one that received 2.5mg of Salagen, another that received 5mg of Salagen and a third group that received a placebo. All patients received their medications q.i.d. for 12 weeks. The results showed that the 5mg dose was most effective, increasing salivary flow by two to three times and causing significant improvement in dry eye and dry mouth.21

Another study examined the effects of Salagen on dry eye.22 Patients treated with Salagen showed significant improvement in vital dye staining. Also, their answers to a patient questionnaire showed that their dry eye improved.

**Side effects.** The primary side effects of Salagen include sweating, nausea, headache and vomiting.22 Because Evoxac causes significantly fewer side effects and patients have reported equal results for Evoxac and Salagen, I prefer to prescribe Evoxac for patients who have Sjögren’s syndrome.
Contraindications. Patients who have asthma, narrow-angle glaucoma, stomach ulcers, hypertension and potential heart conditions should not take Salagen.23

Because ocular surface disease and dry eye are some of the most common pathologies that we manage, understanding the role of oral medications will enhance our treatment capabilities.

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